CADTH

CADTH Common Drug Review

# Clinical Review Report

## AMIFAMPRIDINE (RUZURGI)

## (Médunik Canada Inc.)

**Indication:** For the symptomatic treatment of Lambert-Eaton myasthenic syndrome in patients 6 years of age and older.


| | |
|---|---|
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# Abbreviations

| | |
|---|---|
| **3TUG** | Triple Timed Up-and-Go |
| **ADL** | activities of daily living |
| **AE** | adverse event |
| **CMAP** | compound muscle action potential |
| **CI** | confidence interval |
| **CP** | coverage probability |
| **HRQoL** | health-related quality of life |
| **ITT** | intention to treat |
| **IVIg** | intravenous immunoglobulin |
| **LEFS** | Lower Extremity Functional Scale |
| **LEMS** | Lambert-Eaton myasthenic syndrome |
| **MG** | myasthenia gravis |
| **MID** | minimal important difference |
| **MRC** | Medical Research Council |
| **PP** | per protocol |
| **QMG** | quantitative myasthenia gravis |
| **SAE** | serious adverse event |
| **SCLC** | small cell lung cancer |
| **SD** | standard deviation |
| **SE** | standard error |
| **SF-36** | Short-Form (36) Health Survey |
| **W-SAS** | self-assessment of LEMS-related weakness |

# Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

## Table 1: Submitted for Review

| Item | Description |
|---|---|
| **Drug product** | Amifampridine (Ruzurgi) tablets, 10 mg |
| **Indication** | For the symptomatic treatment of LEMS in patients 6 years of age and older |
| **Reimbursement request** | As per indication |
| **Health Canada approval status** | NOC |
| **Health Canada review pathway** | Priority review |
| **NOC date** | August 10, 2020 |
| **Sponsor** | Médunik Canada Inc. |

LEMS = Lambert-Eaton myasthenic syndrome; NOC = Notice of Compliance.

## Stakeholder Engagement

The information in this section is a summary of input provided by the patient groups that responded to CADTH's call for patient input and from the clinical experts consulted by CADTH for the purpose of this review.

### Patient Input

In the absence of patient group input, 1 testimonial from a Canadian individual with LEMS was accepted for this CADTH review, given the rarity of LEMS in Canada.

The patient highlighted symptoms of LEMS, including worsening arm, core, and leg strength; dry mouth and difficulty swallowing; muscle weakness; and becoming fall-prone. The patient specified that their disease experience led to their inability to continue working.

The patient was initially treated with pyridostigmine and then amifampridine. Treatment with amifampridine was reported to increase the patient's mobility and independence (e.g., ability to rise from a seated position without assistance, ability to navigate stairs safely) and symptoms (e.g., improvement in dry mouth and swallowing).

The patient's testimonial highlighted the desire for improvement in muscle strength and bodily functions with the goal of performing daily activities with a sense of normalcy.

### Clinician Input

The clinical experts consulted by CADTH for this review identified access to amifampridine as the main unmet need for patients with LEMS, given that amifampridine has historically been accessed through compassionate use by the sponsor.

The clinical experts consider amifampridine to be the first-line therapy for the treatment of LEMS. The clinical experts consulted by CADTH agreed that there is no acceptable alternative to amifampridine for the symptomatic treatment of LEMS. Despite the poorer prognosis of patients who have the paraneoplastic form of LEMS, the clinical experts stated that all patients with LEMS should have access to amifampridine.

Improvement in health-related quality of life (HRQoL) and functional ADLs is the ultimate goal of treatment for patients with LEMS, based on feedback from the clinical experts consulted by CADTH. The ideal assessment of treatment effect consists of the patient's subjective response, a neurological exam, the Triple-Timed Up-and-Go (3TUG) test (or alternative assessment), and an electrophysiological study. However, variability in clinicians' assessment of response to treatment is noted in the Canadian clinical setting.

The diagnosis and treatment of patients with LEMS is overseen by a specialist in neurology. Assessment of response to treatment with amifampridine typically involves assessment at baseline (pre-treatment), once within the first month (typically within 1 week or week 2 of initiation), and every 3 months until it is perceived by the treating clinician that the patient's symptoms are being managed appropriately.

Panellists stated that patients who respond to treatment with amifampridine are expected to continue treatment throughout their lives. Patients who discontinue treatment with amifampridine include those whose symptoms do not improve based on a combination of the following: patient's subjective response, objective neurological exam, 3TUG test (or alternative assessment), and electrophysiological study.

## Introduction

### Disease Background

Lambert-Eaton myasthenic syndrome (LEMS) is a rare autoimmune disorder of the neuromuscular junction.[1-3] In approximately 90% of diagnosed patients, LEMS occurs as a result of the production of antibodies against the P/Q-type voltage-gated calcium channels; this ultimately prevents muscle contraction.[3-5] There are 2 forms of LEMS: paraneoplastic and primary autoimmune. Approximately 50% to 60% of LEMS cases are paraneoplastic; these are most commonly associated with small cell lung cancer (SCLC).[1,6] LEMS associated with other autoimmune diseases is referred to as primary autoimmune LEMS.[2] Symptoms associated with both forms of LEMS include proximal muscle weakness, autonomic disturbance, and depressed tendon reflexes.[1,2,5] Patients with LEMS often initially present in clinic with weakness in their legs, and in some cases, difficulty walking.[2] According to the patient input received for this review, LEMS negatively affects all areas of patients' lives. The key concerns raised in the patient input included issues related to impaired muscle strength, impaired bodily functions, and difficulty performing activities of daily living (ADLs).

The estimated incidence of LEMS ranges from 0.2 to 0.5 per million; its prevalence ranges from 2.3 to 2.6 per million based on published studies from Denmark,[7] the Netherlands,[8,9] and the US.[10] There are no published Canadian epidemiological data on LEMS; however, the clinical experts consulted by CADTH anticipate that the incidence and prevalence of LEMS in Canada is similar to estimates from other countries.

Amifampridine has been used as a first-line therapy for both paraneoplastic and primary autoimmune LEMS in Canada and internationally for more than 30 years for symptomatic treatment even though it was not commercially available in Canada until 2020. Amifampridine has historically been accessed through Health Canada's Special Access Program or through compassionate use by the sponsor. Other medications and procedures that may be used in combination with amifampridine include pyridostigmine, immunosuppressants or immunomodulating drugs, steroids, intravenous immunoglobulin (IVIg), and plasma exchange.

Amifampridine is indicated for the symptomatic treatment of LEMS in patients 6 years of age and older. It is available as 10 mg tablets for oral administration. The recommended maximum total daily maintenance dose for patients weighing less than 45 kg is 40 mg. For patients weighing 45 kg or more, the maximum total daily maintenance dose is 80 mg.

The objective of this report is to perform a systematic review of the beneficial and harmful effects of amifampridine (10 mg tablets) for oral administration for the symptomatic treatment of LEMS in patients 6 years of age and older.

## Clinical Evidence

### Pivotal Studies and Protocol Selected Studies

*Description of Studies*

One pivotal study, DAPPER (N = 32), was included in the CADTH systematic review. DAPPER was a phase II, multi-centre, randomized, double-blind, placebo-controlled withdrawal study that aimed to confirm the safety and evaluate the efficacy of amifampridine for the treatment of weakness associated with LEMS in adult patients. Patients with known clinically active LEMS who had continuous, stable use of amifampridine for at least 3 months were enrolled. Patients on other LEMS-related treatments (in addition to amifampridine) were required to be on a stable regimen for at least 3 months. Patients were required to be responsive to amifampridine, defined as being able to experience an unequivocal improvement in a LEMS-induced dysfunction within 15 minutes to 30 minutes after taking their first dose in the morning. Patients were excluded from DAPPER if they did not display a sufficiently large response to amifampridine during the baseline observation period.

DAPPER was composed of 3 stages. Stage 1 involved 2 days of baseline assessments. Patients who had a sufficient response to amifampridine (as indicated by the 3TUG test) and were eligible to enroll in DAPPER entered stage 2, where they were centrally randomized in a 1:1 ratio to continue their current treatment regimen (group A, continuous amifampridine) or withdraw from amifampridine (group B, taper to placebo) for up to 3 and a half days. Patients in the placebo arm had their baseline amifampridine tapered over a 72-hour period followed by approximately 16 hours of placebo with no amifampridine. Baseline amifampridine was restored during stage 3, in which patients were observed for half a day or until clinically stable.

The primary efficacy end point in DAPPER 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 2) when compared with the time-matched average of the 3TUG assessments during stage 1. In DAPPER, this was categorized as a deterioration of greater than 30% in 3TUG time. The secondary efficacy end point in DAPPER was the self-assessment of LEMS-related weakness (W-SAS), which was conducted at the end of stage 2 compared to the baseline.

The baseline characteristics were generally balanced between the randomized treatment arms in DAPPER. Patients included in DAPPER had a mean age of 50.7 (standard deviation [SD] = 15.97) and 59.3 (SD = 14.99) in the amifampridine and placebo arms, respectively. Female patients accounted for 71.4% (amifampridine) and 61.1% (placebo) of the population in each arm. One patient in the placebo arm had paraneoplastic syndrome. The mean duration of LEMS diagnosis prior to randomization was 6.7 years in each arm.

Baseline use of amifampridine and other LEMS medications was similar between the treatment arms.

*Efficacy Results*

In DAPPER, disability progression was assessed using the 3TUG test, W-SAS, compound muscle action potential (CMAP) assessment, and the Lower Extremity Functional Scale (LEFS). LEMS-related ADLs were used as a functional measurement in DAPPER. Of these assessed outcomes, statistical analyses were conducted for only the 3TUG and W-SAS.

In DAPPER, the primary efficacy outcome assessment demonstrated that significantly more patients in the taper-to-placebo arm exhibited a deterioration of 30% or greater on the 3TUG test compared to those in the continuous-amifampridine arm. None of the patients (0%) in the continuous-amifampridine arm had a 30% or greater deterioration in the final (blinded) 3TUG test after withdrawal of the study drug (stage 2) compared to 72.2% (n = 13) of patients in the taper-to-placebo arm ($P < 0.0001$). The treatment effect based on the 3TUG test favoured continuous amifampridine. According to the clinical experts consulted by CADTH, the 3TUG test is considered a preferred component in assessing treatment response in patients with LEMS in clinic. The assessment of this outcome was based on a threshold of 30% or greater deterioration in 3TUG time, which is clinically relevant, based on the literature and input from the clinical experts consulted for the CADTH review.[11]

The secondary efficacy end point in DAPPER, the W-SAS, provided a global self-assessment that demonstrated an increase in weakness in the taper-to-placebo arm compared to the continuous-amifampridine arm. The mean W-SAS final score was greater among patients in the continuous-amifampridine arm compared to those in the taper-to-placebo arm (–0.2 [SD = 1.19] versus –2.4 [SD = 0.85]; $P < 0.0001$). Inference for this secondary outcome is limited, given that it was not adjusted for multiple comparisons; this prevents firm conclusions from being drawn. No minimal important difference (MID) for patients with LEMS was identified in the literature; however, the clinical experts consulted by CADTH determined that the results were clinically meaningful and similar to the assessments of patients' subjective responses to treatments that are used in clinic.

Outcomes for CMAP, LEFS, and LEMS-related ADLs were reported descriptively without performing formal statistical testing. As a phase II trial, DAPPER was not designed to test multiple outcomes and did not have a statistical testing framework;[12] therefore, firm conclusions cannot be drawn based on the assessments of outcomes for CMAP, LEFS, and LEMS-related ADLs. However, the clinical experts consulted by CADTH were of the view that the descriptive results of the CMAP, LEFS, and LEMS-related ADLs were clinically relevant and supported the primary and secondary efficacy outcomes.

LEMS-related symptoms, HRQoL, and outcomes related to productivity were also of importance to patients, based on the input received for this review. These outcomes were not assessed in DAPPER; thus, the efficacy of amifampridine with respect to HRQoL and productivity remains unknown.

Subgroup analyses based on type of LEMS (paraneoplastic versus primary autoimmune) and age (pediatric versus adult patients) were not performed in DAPPER. Whether or not the treatment effect differs between the subgroups identified as relevant in the CADTH review protocol remains unknown.

*Harms Results*

In DAPPER, adverse events (AEs) excluding LEMS-related signs and symptoms occurred in 5 patients (35.7%) in the continuous-amifampridine arm and in 12 patients (66.7%) in the taper-to-placebo arm. The most common AEs were abdominal discomfort and respiratory tract infection, each of which occurred in 2 patients (11.1%) in the taper-to-placebo arm. AEs attributed to LEMS-related signs and symptoms occurred in 2 patients (14.3%) in the continuous-amifampridine arm and in 6 patients (33.3%) in the taper-to-placebo arm. The most common AEs were decreased oxygen saturation (N = 3, 16.7%), muscle spasms (N = 2, 11.1%), and nausea (N = 2, 11.1%), each of which occurred in patients in the taper-to-placebo arm.

In DAPPER, 1 patient (5.6%) in the taper-to-placebo arm experienced a serious adverse event (SAE) (severe pneumonia). Two patients in the taper-to-placebo arm withdrew from treatment due to AEs attributed to LEMS-related signs and symptoms: decreased oxygen saturation (5.6%) and anxiety (5.6%). One patient (5.6%) in the taper-to-placebo arm experienced prolonged QT assessed through electrocardiogram, and 1 patient (5.6%) in the taper-to-placebo arm experienced paresthesia. Seizures were not reported in DAPPER. No deaths were reported during DAPPER.

The duration and design of DAPPER were limited and may not be a true reflection of the harms associated with amifampridine for all patients with LEMS. The patients included in DAPPER were not amifampridine-naive. They were required to be on a stable and optimized dose of amifampridine and meet a threshold of responsiveness to amifampridine at baseline.

## Table 2: Summary of Key Results From Pivotal Study

| | DAPPER | |
|---|---|---|
| | Continuous amifampridine N = 14 | Taper to placebo N = 18 |
| **Category of change in 3TUG (> 30% deterioration)[a-c]** | | |
| Category A to category B (no change or faster) | 14 (100.0%) | 5 (27.8%) |
| Category C to category G (> 30% slower) | 0 (0.0%) | 13 (72.2%) |
| P value | < 0.0001 | |
| **Category of change in 3TUG[d]** | | |
| A: > 30% faster | 0 (0.0%) | 0 (0.0%) |
| B: No change | 14 (100%) | 5 (27.8%) |
| C: > 30% to 50% slower | 0 (0.0%) | 5 (27.8%) |
| D: > 50% to 100% slower | 0 (0.0%) | 5 (27.8%) |
| E: > 100% to 200% slower | 0 (0.0%) | 1 (5.6%) |
| F: > 200% slower | 0 (0.0%) | 2 (11.1%) |
| G: Cannot perform TUG | 0 (0.0%) | 0 (0.0%) |
| P value | 0.0008 | |
| **Final W-SAS score[a,e,f]** | | |
| n | 14 | 18 |
| Mean (SD) | –0.2 (1.19) | –2.4 (0.85) |

| | DAPPER | |
|---|---|---|
| | Continuous amifampridine N = 14 | Taper to placebo N = 18 |
| Median (range) | 0.0 (-3.0 to 2.0) | –3.0 (–3.0 to 0.0) |
| P value | < 0.0001 | |
| **Final W-SAS category,[a,e,f] N (%)** | | |
| Much weaker (–3) | 1 (7.1%) | 10 (55.6%) |
| Much weaker (–2) | 1 (7.1%) | 6 (33.3%) |
| Somewhat weaker (–1) | 1 (7.1%) | 1 (5.6%) |
| About the same (0) | 9 (64.3%) | 1 (5.6%) |
| Somewhat stronger (1) | 1 (7.1%) | 0 (0.0%) |
| Much stronger (2) | 1 (7.1%) | 0 (0.0%) |
| Much stronger (3) | 0 (0.0%) | 0 (0.0%) |
| P value | < 0.0001 | |
| **Harms excluding LEMS-related signs and symptoms,[g] n (%)** | | |
| Adverse events | 5 (35.7%) | 12 (66.7%) |
| Serious adverse events | 0 | 1 (5.6%) |
| Patients who stopped treatment due to adverse events | 0 | 0 |
| Deaths | 0 | 0 |
| Notable harms | | |
| Clinically significant electrocardiogram | 0 | 0 |
| Electrocardiogram QT prolonged | 0 | 1 (5.6%) |
| Paresthesia | 0 | 1 (5.6%) |
| Seizures | NR | NR |
| **LEMS-related signs and symptoms,[g] n (%)** | | |
| Adverse events | 2 (14.3%) | 6 (33.3%) |
| Serious adverse events | 0 | 0 |
| Patients who stopped treatment due to adverse events | 0 | 2 (11.1%) |
| Deaths | 0 | 0 |

3TUG = Triple-Timed Up-and-Go; LEMS = Lambert-Eaton myasthenic syndrome; NR = not reported; SD = standard deviation; TUG = Timed Up-and-Go; W-SAS = self-assessment of LEMS-related weakness.

[a] Efficacy population.

[b] Definition of the categories: A: greater than 30% faster; B: 30% slower to 30% faster; C: greater than 30% to 50% slower; D: greater than 50% to 100% slower; E: greater than 100% to 200% slower; F: greater than 200% slower; G: cannot perform 3TUG.

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

[d] P value based on Cochran-Mantel-Haenszel test.

[e] The last observation during stage 2 served as the final W-SAS.

[f] The P value is based on the Cochran-Mantel-Haenszel test for categorical data and on the t-test for continuous data.

[g] Safety population.

Source: Clinical Study Report for JPC 3,4-DAPPER.[13]

*Critical Appraisal*

The key limitations of the phase II study, DAPPER, related to internal validity issues, such as generalizability and the increased potential for unblinding and descriptive assessment of outcomes.

DAPPER was a double-blind study that employed various strategies to maintain blinding of the patients, investigator, site personnel, and sponsor personnel. However, because the study was designed using a withdrawal enrichment strategy, unblinding was possible, given that patients in the placebo arm were expected to experience deterioration prior to amifampridine being reinstated. Unblinding in DAPPER may have biased subjective patient-assessed (e.g., through the W-SAS and LEFS) and investigator-assessed (e.g., through LEMS-related ADLs) outcome results in favour of amifampridine.

Outcomes for CMAP, LEFS, and LEMS-related ADLs were reported descriptively without performing formal statistical testing. As a phase II trial, DAPPER was not designed to test multiple outcomes and did not have a statistical testing framework;[12] therefore, firm conclusions cannot be drawn based on the assessments of outcomes for W-SAS, CMAP, LEFS, and LEMS-related ADLs.

DAPPER was conducted using a withdrawal enrichment strategy. The study design and eligibility criteria led to a study population that consisted of patients who were treatment-experienced and responsive to amifampridine at baseline whose magnitude of treatment response may not be representative of the Canadian amifampridine-experienced population or generalizable to amifampridine-naive patients, including those newly diagnosed with LEMS. While enrichment strategies such as these have been used in the study of rare disease populations, the trial design of DAPPER limits generalizability to patients who may be eligible for treatment with amifampridine as per the Health Canada indication.

## Other Relevant Evidence

The DUKE study was a randomized, placebo-controlled, phase II study designed to evaluate the effectiveness and determine the acute and long-term side effects of amifampridine in adult patients with LEMS. The DUKE study was a reanalysis of a previously published study by Sanders (2000). Twenty-six patients were randomized to receive amifampridine as 10 mg to 20 mg capsules or placebo 3 times or 4 times per day for 6 days to 9 days. The primary efficacy measure was the quantitative myasthenia gravis (QMG) score. Additional efficacy measurements were: change in summated CMAP amplitude; change in swallowing times; and change in walking times. In the intention-to-treat (ITT) population, 57.6% of the study patients were female and 42.3% were male. The median age of LEMS onset was 56.5 years in both treatment groups. There were 4 and 5 patients with SCLC in the amifampridine and placebo groups, respectively.

Two additional studies were identified as relevant evidence from the literature search. The Oh (2009) study was a randomized, double-blind crossover study that investigated the clinical and electrophysiological efficacy of amifampridine in patients with LEMS and used placebo in the other arm of the trial. The Oh (2009) study recruited 8 patients with LEMS (of whom 7 [87.5%] were male) over a 12-year period from 1996 to 2008. All patients had fluctuating leg weakness, proximal leg weakness, and diminished or absent reflexes at the time of diagnosis. Three tablets (30 mg) of amifampridine or placebo were given on the first day of the treatment. The dose was increased to a maximum of 75 mg/day over 3 days in

the 3-day trial and to a maximum of 80 mg over 8 days in the 8-day trial. The main outcomes assessed in the Oh (2009) study[14] were:

- Subjective symptoms score
- LEMS classification
- Medical Research Council (MRC) score
- QMG score
- CMAP

McEvoy (1989) was an open-label, prospective, double-blind, placebo-controlled crossover study of 12 patients with LEMS to determine the efficacy and safety of amifampridine compared to placebo. The study recruited 12 patients, 8 (66.6%) of whom were female; the age of patients ranged from 34 years to 75 years (mean = 65). Seven (58.33%) patients had cancer. The dosage of the study drug was determined based on the maximum tolerable dose identified during the open-label phase of the trial. The main outcomes were:

- neurological disability scores
- isometric strength
- electrophysiological improvement.

*Efficacy Results*

In the DUKE study, the mean (SD) change from baseline for the primary end point (QMG score) was –2.0 (2.16) in the amifampridine group and 0.2 (1.65) in the placebo group (P = 0.015). Consistent with the 3TUG results from DAPPER, the results of the QMG score in DUKE favoured the use of amifampridine. However, the QMG score is not considered an appropriate or relevant assessment tool for LEMS, according to the clinical experts consulted by CADTH.

In the Oh (2009) study, the mean ± standard error (SE) for QMG score change in the amifampridine group was –2.36 ± 2.25 versus 0.40 ± 1.14 in the placebo treatment group (P = 0.0223). The mean ± SE for CMAP score change in the amifampridine group was 1.79 ± 2.05 versus –0.90 ± 1.78 in the placebo treatment group (P = 0.0246).

The McEvoy (1989) study reported that the average resting, facilitated, and decrement CMAP scores during the double-blind phase in the active drug treatment group were 5.1 ± 0.9, 9.6 ± 0.8, and 21.6 ± 2.2 in the arm and 3.2 ± 0.7, 4.9 ± 0.9, and 20.4 ± 2.6 in the leg, respectively. In the placebo group, they were 2.8 ± 0.6, 7.6 ± 0.7, and 28.6 ± 3.0 (P < 0.005) in the arm and 1.8 ± 0.4, 3.4 ± 0.7, and 25.8 ± 2.3 P < 0.010 in the leg, respectively.

The Oh (2009) and McEvoy (1989) studies had limitations related to study design that limited their internal validity, including sample sizes, lack of washout period, and failure to control for multiplicity. Neither study provided sufficient detail regarding the methodological design or statistical analysis plan; therefore, a thorough critical appraisal was not possible. Insufficient detail limited CADTH's ability to fully discern generalizability to the Canadian population of patients with LEMS. It was unclear if any of the patients in Oh (2009) were amifampridine-naive. Both Oh (2009) and McEvoy (1989) included patients with paraneoplastic LEMS; however, the limitations of the studies prevent interpretation of the results.

*Harms Results*

In the DUKE study, a retrospective review of safety data conducted by the sponsor revealed that 3 patients reported SAEs: 1 patient who had recently been treated for SCLC and randomized to placebo experienced, anxiety, respiratory difficulties, difficulty speaking, and chest discomfort; 1 patient randomized to amifampridine was hospitalized for muscle weakness about 1 week after completing the study; and 1 patient randomized to placebo died of pulmonary complications related to lung cancer approximately 1 month after starting open-label treatment with amifampridine.

In the Oh (2009) study, 2 patients complained of paresthesia: 1 reported a heat sensation in the body, and 1 reported numbness of the tongue and lips.

In the McEvoy (1989) study, 10 of 12 patients had perioral or acral paresthesias after 30 minutes of administering amifampridine. After 10 months of treatment, 1 patient had a seizure after receiving a maximal dose of 100 mg of amifampridine.

## Conclusions

One phase II, double-blind, placebo-controlled withdrawal study (DAPPER; N = 32) of patients with LEMS demonstrated that continuous treatment with amifampridine resulted in less disability progression compared with patients whose amifampridine was withdrawn. In DAPPER, a greater proportion of patients in the taper-to-placebo arm (72.2%) exhibited a deterioration of 30% or greater on the 3TUG test compared to patients in the continuous-amifampridine arm (0%). The W-SAS provided a global self-assessment that demonstrated increased weakness among patients in the taper-to-placebo arm (mean = –2.4) compared to the continuous-amifampridine arm (–0.2); however, caution is warranted when drawing firm conclusions due to lack of control for multiple comparisons. The effect of amifampridine on HRQoL and productivity was not evaluated in DAPPER and remains unknown. DAPPER was limited by the potential for unblinding and generalizability to the amifampridine-naive patient population. The evidence available from the DUKE study was consistent with the clinical findings from DAPPER.

Evidence gaps for the reviewed studies include the use of amifampridine in amifampridine-naive patients, patients with paraneoplastic LEMS, and pediatric patients.

The harms data obtained from the body of evidence reviewed for the CADTH report are limited. Due to the duration and design of DAPPER, harms reported may not be a true reflection of the harms associated with amifampridine for all patients with LEMS.

# Introduction

## Disease Background

LEMS is a rare autoimmune disorder of the neuromuscular junction.[1-3] In approximately 90% of diagnosed patients, LEMS occurs as a result of the production of antibodies against the P/Q-type voltage-gated calcium channels on the presynaptic membrane at the neuromuscular junction, resulting in a reduction of calcium channels.[1,3,5] This prevents calcium from entering the nerve terminal and triggering the fusion of acetylcholine vesicles with the synaptic membrane. In turn, this prevents the release of acetylcholine into the synaptic cleft, ultimately preventing muscle contraction.[1,3-5]

There are 2 forms of LEMS: paraneoplastic and primary autoimmune. Approximately 50% to 60% of LEMS cases are paraneoplastic; these are most commonly associated with SCLC.[1] Paraneoplastic LEMS typically begins in late adulthood at approximately 60 years of age, and is more common in male patients, although this may relate to the association with SCLC.[6] Patients diagnosed with LEMS are subsequently screened for SCLC, due to its strong association.[1] LEMS associated with other autoimmune diseases is referred to as primary autoimmune LEMS.[2] Primary autoimmune LEMS occurs in patients of all ages, and is more common in female patients.[6]

Symptoms associated with LEMS include proximal muscle weakness, autonomic disturbance, and depressed tendon reflexes.[1,2,5] Patients with LEMS often initially present in clinic with weakness in their legs, and in some cases, difficulty walking.[2] Autonomic disturbances may include dry mouth, constipation, erectile dysfunction, postural hypertension, and sweating. As LEMS progresses, patients may experience weakness of the arms, bulbar issues — such as dysphagia, swallowing difficulties, slurred speech, and weakness of the neck — and ocular issues, such as double vision and droopy eyes.[1,2] According to the patient input received for this review, LEMS negatively affects all areas of life. The key issues raised in the patient input were those related to impaired muscle strength, impaired bodily functions, and difficulty performing ADLs.

In Canada, LEMS is diagnosed by neuromuscular specialists through clinical examination, serum antibody testing (P/Q-type voltage-gated calcium channels), and repetitive nerve stimulation.[1] There are no formal guidelines in Canada for the diagnosis and treatment of LEMS. Some symptoms of LEMS are similar to those associated with myasthenia gravis (MG), and MG may be confused with LEMS if ocular or bulbar symptoms develop first.[1,5] The clinical experts consulted by CADTH identified the potential for misdiagnosis or delayed diagnosis as a result of the rarity of LEMS combined with the subtlety of the symptoms noted in mild cases (e.g., subtle stiffness or weakness in legs). The clinical experts also noted that patients with the paraneoplastic form of LEMS may be underdiagnosed because their symptoms could be attributed to cancer or cancer treatment (e.g., chemotherapy). However, misdiagnoses and delayed diagnoses are thought to have diminished over the past decade due to improved awareness and knowledge of LEMS.[1]

The estimated incidence of LEMS ranges from 0.2 to 0.5 per million; its prevalence ranges from 2.3 to 2.6 per million, based on published studies from Denmark,[7] the Netherlands,[8,9] and the US.[10] LEMS is 46 times less prevalent than MG, whereas the annual incidence rate of LEMS is 14 times lower than MG; this is largely attributed to the poor survival rate of patients with LEMS and SCLC.[8] There are no published Canadian epidemiological data on LEMS; however, the estimates from Denmark, the Netherlands, and the US are considered

by the clinical experts consulted for this review to be comparable to Canada. The clinical experts consulted by CADTH noted that LEMS is very rare in the pediatric population. There are no published Canadian epidemiological data on pediatric LEMS.

## Standards of Therapy

The ultimate treatment goal for patients with LEMS is improvement in HRQoL and functional ADLs.

Amifampridine has been used as a first-line therapy for the symptomatic treatment of both paraneoplastic and primary autoimmune LEMS in Canada and internationally for more than 30 years, even though it was not commercially available in Canada until 2020. Amifampridine has historically been accessed through Health Canada's Special Access Program or through compassionate use by the sponsor. The clinical experts consulted by CADTH agreed that there is no acceptable alternative to amifampridine for the symptomatic treatment of LEMS. Pyridostigmine is a cholinergic drug that acts primarily by inhibiting cholinesterase.[15] It enhances cholinergic action by facilitating the transmission of impulses across neuromuscular junctions.[15] Patients with the primary autoimmune form of LEMS may receive treatment with amifampridine in combination with pyridostigmine. However, pyridostigmine is not considered an alternative form of treatment. According to the clinical experts consulted by CADTH for this review, it is most often used in Canada as a bridging drug for patients diagnosed with LEMS who may be waiting for access to amifampridine. The clinical experts stated that the clinical effectiveness of pyridostigmine is minor in most patients, and that its use is generally discontinued once patients have access to amifampridine.

Other medications and procedures that may be used in combination with amifampridine and/or pyridostigmine include immunosuppressants, immunomodulating drugs, steroids, IVIg, or plasma exchange. According to the clinical experts consulted by CADTH, combination treatment may be considered in patients who do not have an adequate treatment response to amifampridine and/or pyridostigmine. In Canada, the use of IVIg or plasma exchange for the treatment of LEMS is rare.

According to the clinical experts consulted by CADTH, in patients with the paraneoplastic form of LEMS, the underlying malignancy (most often SCLC) is treated first (through surgical resection, radiation, or chemotherapy) or in parallel with amifampridine. Use of immunosuppressive drugs is often avoided in the treatment of paraneoplastic LEMS due to the potential to increase the likelihood of dissemination of the underlying SCLC; otherwise, treatment of paraneoplastic LEMS is generally similar to treatment of primary autoimmune LEMS.

According to the clinical experts consulted by CADTH, pediatric patients are generally treated similarly to adult patients, given that the pathophysiology of LEMS is the same.

## Drug

Amifampridine or 3,4-diaminopyridine is a broad-spectrum potassium channel blocker. The exact mechanism by which amifampridine exerts its therapeutic effect in patients with LEMS has not been fully elucidated.[16] Blocking potassium channels results in blocking the efflux of potassium ions, thereby prolonging the duration of the presynaptic action potential.[4,17] This allows more voltage-gated calcium channels to open, increasing the entry of calcium into the nerve terminal.

Amifampridine is indicated for the symptomatic treatment of LEMS in patients 6 years of age and older. Amifampridine was granted priority review by Health Canada and received a Notice of Compliance on August 10, 2020.

Dosing should be individualized based on disease severity, patient response, and patient population.[16] The dose should be titrated gradually to the optimal effective dose with the minimum of side effects.[16] Once achieved, this optimal dose should be maintained, and dosing frequency should be adjusted as needed.[16] The recommended dosage regimen of amifampridine 10 mg tablets for oral administration is presented in Table 3.

## Table 3: Recommended Dosage of Amifampridine for Patients 6 Years of Age and Older

| Age and body weight | Initial dose | Titration regimen | Maximum recommended single dose | Maximum total daily maintenance dose |
|---|---|---|---|---|
| All patients weighing less than 45 kg | 5 mg to 10 mg daily in divided doses (2 to 3 times per day) | Increase daily in increments of 2.5 mg to 5 mg, divided in up to 5 doses per day | 10 mg | 40 mg |
| All patients weighing 45 kg or more | 10 mg to 20 mg daily in divided doses (2 to 3 times per day) | Increase daily in increments of 5 mg to 10 mg, divided in up to 5 doses per day | 20 mg | 80 mg<br>Some patients may benefit from a total daily dose of 100 mg. |

Source: Product monograph for Ruzurgi.[16]

# Stakeholder Engagement

## Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups.

### About the Patient Groups and Information Gathered

No patient group input was received following CADTH's call for patient input. Given the rarity of LEMS in Canada, CADTH accepted a testimonial from a Canadian individual who described their experience with LEMS.

### Disease Experience

The patient who provided input for this submission reported that they were diagnosed with LEMS 1 year following worsening arm, core, and leg strength. Their symptoms included dry mouth, difficulty swallowing, muscle weakness, and becoming fall-prone. Eventually, due to the disease, the patient had to discontinue work as a teacher. At 37 years old, the patient remembers thinking:

*"I would eventually end up in a wheelchair or be bedridden. It was pretty bleak."*

### Experience With Treatment

Before diagnosis of LEMS, the patient reported being treated with IVIg therapy, which did not have any significant effect on their condition. The therapy led to the patient being severely ill and losing their white blood cells.

The patient was given pyridostigmine for treatment; however, the patient did not show significant improvement with the treatment.

The treating specialist was able to access and prescribe amifampridine for the patient. Following treatment with this drug, the patient noticed improved effects, particularly a greater ability to rise from a seated position without assistance, fewer dry mouth and swallowing symptoms, and a greater ability to navigate stairs safely without holding both railings. The patient was also using azathioprine, an immunosuppressive medication.

The patient stated:

"To say this drug is a blessing and *does miracles is not overstating the results."*

*"My close friends and family have since told me they feared for my life when I was at my weakest, and celebrated my return to almost normal."*

*"The combination of these medicat*ions has given me a new lease on life and I am so grateful to have access to this medicine."

### Improved Outcomes

The patient was hopeful that the drug under review would help improve their muscle strength and other bodily functions, thereby allowing them to perform daily activities with a sense of normalcy.

The patient identified that the cost of the drug is a main concern, as they believe the drug would be unaffordable (and access may be restricted) if it is not reimbursed. The patient is emphatic about the need for continued and affordable access to amifampridine.

## Clinician Input

All CADTH review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol; assisting in the critical appraisal of clinical evidence; interpreting the clinical relevance of the results; and providing guidance on the potential place in therapy). As part of the amifampridine review, a panel of 5 clinical experts from across Canada was convened to characterize unmet therapeutic needs, assist in identifying and communicating situations where there were gaps in the evidence that could be addressed through the collection of additional data, promote the early identification of potential implementation challenges, gain further insight into the clinical management of patients living with the condition, and explore the drug's potential place in therapy (e.g., potential reimbursement conditions). A summary of this panel discussion is presented in this section.

### Unmet Needs

The panelists stated that amifampridine has been used in Canada and internationally for more than 30 years for the symptomatic treatment of LEMS. In Canada, amifampridine has not been commercially available to patients. It has historically been accessed through compassionate use by the sponsor. Access is a challenge for patients.

### Place in Therapy

The panelists consider amifampridine to be the first-line therapy for the treatment of LEMS. It has been used alone and in combination with other treatments or therapies (e.g., pyridostigmine, immunosuppressants or immunomodulating drugs, steroids, or IVIg) for the past 30 years. These other treatments are generally considered by panelists to be insufficiently effective and associated with adverse effects. Panelists agree that there are no acceptable alternatives to amifampridine that are currently available. The recent approval of amifampridine by Health Canada is unlikely to cause a shift in the treatment paradigm; panelists expect it to remain the first-line therapy for the treatment of LEMS symptoms.

### Patient Population

Patients with LEMS can be broadly classified as paraneoplastic or primary autoimmune. While patients with the paraneoplastic form of LEMS are known to have a poorer prognosis than patients with the primary autoimmune form, panelists agree that all patients with LEMS should have access to amifampridine. The severity of LEMS ranges from mild to severe. There is no formal classification of severity.

### Assessing Response to Treatment

Panelists agreed that improvement in HRQoL and functional daily activities is the ultimate goal of treatment for patients with LEMS. The ideal assessment includes the patient's subjective response (i.e., whether the patient thinks they are better), an objective

neurological exam (e.g., testing of cranial nerves, strength, and reflexes), the 3TUG test (or alternative assessment), and an electrophysiological study (e.g., CMAP amplitude before and after maximum voluntary contraction).

Panelists noted that relying solely on a neurological exam may be problematic because such an exam does not always represent the patient's functional experience (e.g., the ability to move from a seated position to a standing position and walk). However, it was noted that some clinics are limited to standard neurological exams to determine treatment response because they do not have the capacity to do timed assessments or more comprehensive exams of patients' day-to-day function. The diagnosis and treatment of LEMS is not formally informed by any clinical practice guidelines. Additionally, the resources that neuromuscular clinics have to assess treatment response vary within Canada. These 2 components may contribute to variability in clinicians' assessment of response to treatment in the Canadian clinical setting.

Assessment of response to treatment with amifampridine typically involves an assessment at baseline (pre-treatment), another within the first month (typically within 1 week or 2 weeks of initiation), and every 3 months until it is perceived by the treating clinician that the patient's symptoms are being appropriately managed. Patients are then seen regularly once a year. Panellists report that the onset of benefit of amifampridine often occurs within hours; however, they reported that they often wait a few weeks for a patient to decide if they perceive a benefit. Panellists suggested that it may take 2 months to 3 months to determine the ideal dosing regimen with amifampridine.

### Discontinuing Treatment

Panelists stated that patients who respond to treatment with amifampridine are expected to continue treatment with amifampridine throughout their lives. Patients who discontinue treatment with amifampridine are those whose symptoms do not improve based on a combination of the following: patient's subjective response, objective neurological exam, 3TUG test (or alternative assessment), and electrophysiological study.

### Prescribing Conditions

The diagnosis and treatment of patients with LEMS is overseen by neuromuscular specialists, many of whom work in specialized neuromuscular clinics; this may be a limiting factor for patients in rural settings.

### Additional Considerations

Panelists highlighted the importance of access to and affordability of amifampridine and agreed that there is no acceptable alternative for the symptomatic treatment of LEMS.

# Clinical Evidence

The clinical evidence included in the review of amifampridine is presented in 3 sections. The first section, the Systematic Review, includes pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as studies that were selected according to an a priori protocol. The second section includes additional relevant studies that were considered to address important gaps in the evidence included in the systematic review. No indirect evidence met the inclusion criteria for this review.

## Systematic Review (Pivotal and Protocol Selected Studies)

### Objectives

To perform a systematic review of the beneficial and harmful effects of amifampridine (10 mg tablets) for oral administration for the symptomatic treatment of LEMS in patients 6 years of age and older.

### Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those meeting the selection criteria presented in Table 4.

**Table 4: Inclusion Criteria for the Systematic Review**

| | |
|---|---|
| **Patient population** | Patients with LEMS 6 years of age and older<br><br>Subgroups:<br>• Pediatric vs. adult patients<br>• Paraneoplastic LEMS vs. primary autoimmune LEMS<br>• Disease severity |
| **Intervention** | Amifampridine 10 mg tablets, administered orally<br>• Patients < 45 kg:<br>  ○ Initial dose: 5 mg to 10 mg daily<br>  ○ Titration regimen: increase daily in 2.5 mg to 5 mg increments, divided in up to 5 doses per day<br>  ○ Maximum recommended single dose: 10 mg<br>  ○ Maximum total daily maintenance dose: 40 mg<br>• Patients ≥ 45 kg:<br>  ○ Initial dose: 10 mg to 20 mg daily<br>  ○ Titration regimen: increase daily in 5 mg to 10 mg increments, divided in up to 5 doses per day<br>  ○ Maximum recommended single dose: 20 mg<br>  ○ Maximum total daily maintenance dose: 80 mg |
| **Comparators** | Administered alone or in combination:<br>• Pyridostigmine[a]<br>• Best supportive care<br>• Placebo |
| **Outcomes** | **Efficacy outcomes:**<br>• Disability progression[b] (e.g., muscle strength, compound muscle action potential, mobility)<br>• Activities of daily living[b]<br>• LEMS-related symptoms[b] (e.g., dry mouth, dry eyes, constipation, impotence, decreased sweating, weight loss)<br>• HRQoL[b]<br>• Productivity[b] (e.g., ability to attend work, school) |

| | |
|---|---|
| | **Harms outcomes:**<br>AEs, SAEs, WDAEs, mortality, notable harms (i.e., seizures, paresthesia, change in echocardiogram) |
| **Study design** | Published and unpublished phase III and IV RCTs |

AE = adverse event; HRQoL = health-related quality of life; LEMS = Lambert-Eaton myasthenic syndrome; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event; vs. = versus.

[a] This drug does not have a Health Canada indication for the treatment of patients with LEMS.

[b] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[18]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) through Ovid and Embase (1974–) through Ovid. The search strategy was composed of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Ruzurgi (amifampridine) and LEMS. Clinical trial registries were searched: the US National Institutes of Health's clinicaltrials.gov, World Health Organization's International Clinical Trials Registry Platform (ICTRP) search portal, Health Canada's Clinical Trials Database, and the European Union Clinical Trials Register.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on November 3, 2020. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee on March 17, 2021.

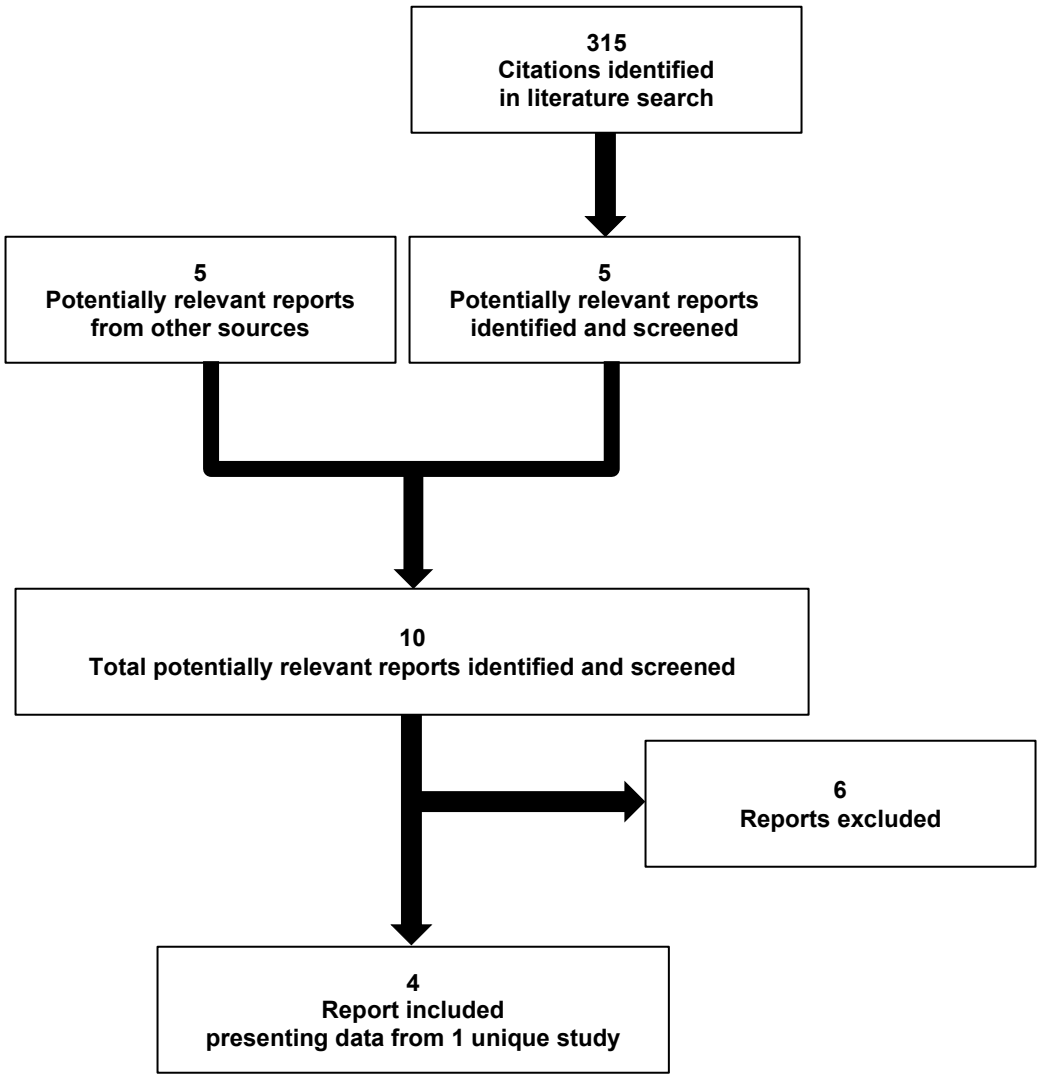
Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the CADTH checklist, *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* (https://www.cadth.ca/grey-matters):[19] Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Clinical Trials Registries, and Databases (Free). Google was used to search for additional internet-based materials. These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts. In addition, the drug sponsor was contacted for information regarding unpublished studies. See Appendix 1 for more information on the grey literature search strategy.

Two CADTH clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least 1 reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

## Findings From the Literature

One study was identified from the literature for inclusion in the systematic review (Figure 1). The included study is summarized in Table 5. A list of excluded studies is presented in Appendix 2.

## Figure 1: Flow Diagram for Inclusion and Exclusion of Studies



## Table 5: Details of Included Studies

| | | DAPPER |
|---|---|---|
| Designs and Populations | **Study design** | Phase II, DB, placebo-controlled, withdrawal RCT |
| | **Locations** | 7 centres in the US |
| | **Randomized (N)** | 32 |
| | **Inclusion criteria** | • ≥ 18 years of age<br>• Ambulatory while taking amifampridine (i.e., the patient was able to perform the TUG, either with or without an assistive device)<br>• Established diagnosis of LEMS<br>• Continuous use of amifampridine for at least 3 months<br>• Minimum of 3 doses of amifampridine per day, with no single dose < 10 mg<br>• The patient needed to wait about 15 minutes to 30 minutes to experience an unequivocal improvement in a LEMS-induced dysfunction after taking their first dose of amifampridine in the morning<br>• Stable regimen of all LEMS-related treatments for at least 3 months |
| | **Exclusion criteria** | • Last monoclonal antibody treatment (e.g., rituximab) within the preceding 6 months<br>• Clinically significant or poorly controlled condition that, in the opinion of study personnel, might have posed an unacceptable risk to the patient if they entered into the study<br>• Respiratory failure requiring intubation while on amifampridine with no precipitating event or medication<br>• Current use of other aminopyridines (e.g., 4-AP) or guanidine<br>• Did not display a sufficiently large response to amifampridine during the baseline observation period in the clinical research unit to detect a decline during withdrawal of amifampridine |
| Drugs | **Intervention** [a] | Amifampridine tablets, total daily dose of 30 mg/day to 100 mg/day |
| | **Comparator** [a] | Matched placebo tablets |
| Duration | **Phase** | |
| | Stage 1 (baseline) | 2 days |
| | Stage 2 (withdrawal) | Up to 3.5 days |
| | Stage 3 (reinstitute) | ~0.5 days; up to 2 additional days if needed |
| | Follow-up | 4 weeks |
| Outcomes | **Primary end point** | Categorization of the degree of change in the 3TUG test upon withdrawal of active medication (> 30% deterioration in 3TUG time) |
| | **Secondary and exploratory end points** | **Secondary:**<br>• W-SAS<br>**Exploratory:**<br>• CMAP<br>• Change in 3TUG and CMAP scores during down-titration period<br>• Onset and nature of LEMS-related signs and symptoms after withdrawal<br>• 50% or more deterioration in the 3TUG score during stage 2<br>• 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<br>• Comparison of morning 3TUG time with nadir 3TUG time later in the same day<br>• Evaluation of 3TUG times at each of the time points during the day<br>• Physician assessment of treatment effect<br>• Recovery in W-SAS, 3TUG, CMAP, and LEMS-related signs and symptoms after reinstituting original treatment regimen (stage 3) |

| | | DAPPER |
|---|---|---|
| | | • Rescue, early advance, and withdrawal from stage 2 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)<br>• LEMS-related ADLs<br>• LEFS<br>• Recovery on each of the end points available after reinstituting the original treatment regimen (stage 3)<br>• Cardiac ejection fraction |
| Notes | **Publications** | Sanders, 2018 |

3TUG = Triple-Timed Up-and-Go; 4-AP = 4-aminopyridine; ADLs = activities of daily living; CMAP = compound muscle action potential; DB = double-blind; LEFS = Lower Extremity Functional Scale; LEMS = Lambert-Eaton myasthenic syndrome; RCT = randomized controlled trial; TUG = Timed Up-and-Go; W-SAS = self-assessment of LEMS-related weakness.

Note: Two additional reports were included (CADTH submission[20] and Health Canada's Reviewers Report[21]).

[a] Stage 2 of study.

Source: Clinical Study Report for JPC 3,4-DAPPER.[13]

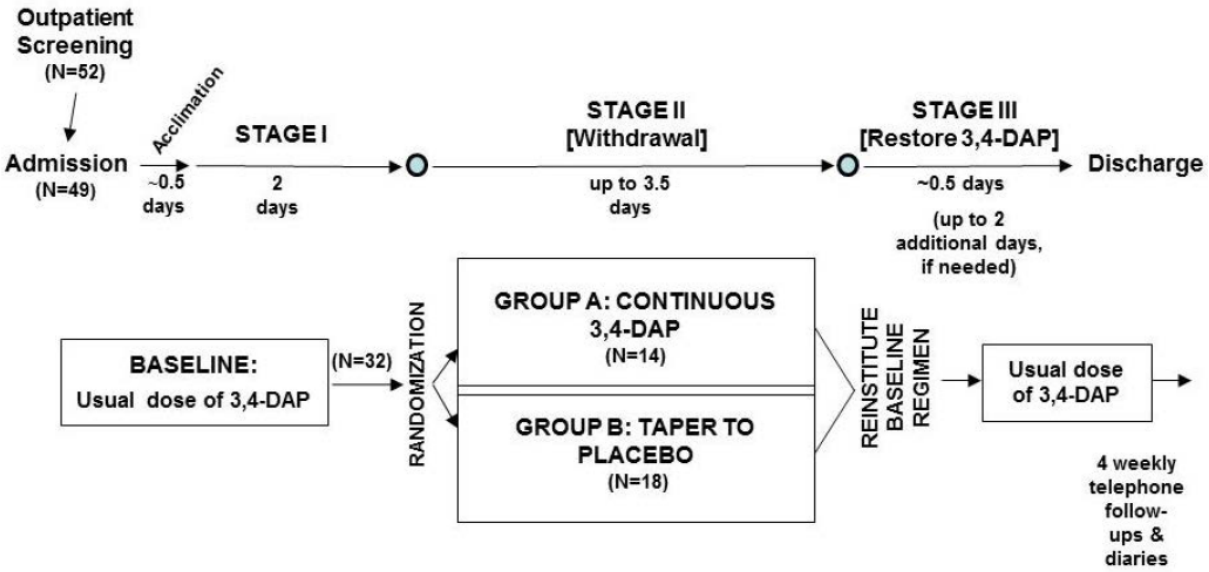
## Description of Studies

One pivotal trial, DAPPER (N = 32), was included in the CADTH systematic review. Details of DAPPER are provided in Table 5.

DAPPER was a phase II, multi-centre, randomized, double-blind, placebo-controlled withdrawal study that aimed to confirm the safety and evaluate the efficacy of amifampridine for the treatment of weakness associated with LEMS in adult patients with known clinically active LEMS who had continuous, stable use of amifampridine for at least 3 months. DAPPER was conducted between February 9, 2012 and March 14, 2014 at 7 investigative sites in the US.

DAPPER was composed of 3 stages (Figure 2). Patients who were potentially eligible for inclusion underwent acclimation for approximately half a day. After acclimation, patients entered stage 1, in which they underwent baseline assessments for 2 days. Patients who had sufficient response to amifampridine as indicated by the 3TUG and were eligible for enrolment in DAPPER (see Inclusion and Exclusion Criteria later in this section) entered stage 2, in which they were centrally randomized in a 1:1 ratio to continue their current treatment regimen (group A, continuous amifampridine) or to withdraw from amifampridine (group B, taper to placebo) for up to 3 and a half days. Randomization was stratified into 4 groups according to baseline treatment with pyridostigmine (yes or no) and use of immunomodulators, immunosuppressants, or steroids (yes or no). Patients in the placebo arm had their baseline amifampridine tapered over a 72-hour period followed by approximately 16 hours of placebo with no amifampridine (Figure 3). Baseline amifampridine was restored during stage 3, in which patients were observed for half a day or until they were clinically stable. Follow-up through telephone and diaries was performed for 4 weeks following discharge.

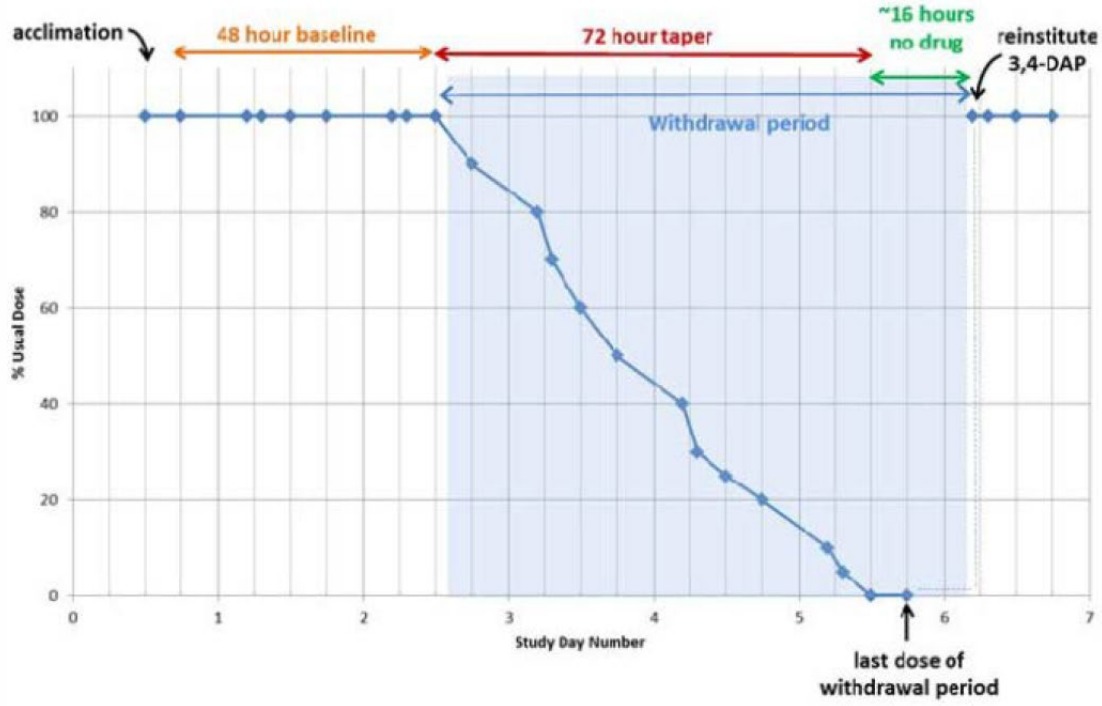
## Figure 2: Study Design for DAPPER




3,4-DAP = 3,4-diaminopyridine

Source: Clinical Study Report for JPC 3,4-DAPPER.[13]

## Figure 3: Stages 1, 2, and 3 and Amifampridine Taper Scheme




3,4-DAP = 3,4-diaminopyridine

Source: Clinical Study Report for JPC 3,4-DAPPER.[13]

### Populations

#### *Inclusion and Exclusion Criteria*

Detailed inclusion and exclusion criteria for DAPPER are presented in Table 5. DAPPER was conducted in adult patients 18 years of age and older with an established diagnosis of LEMS. Patients had to be ambulatory while on their usual dose of amifampridine. Patients had to be on stable regimens of amifampridine and other LEMS-related treatments (if applicable) for at least 3 months. Patients needed to be able to experience an unequivocal improvement in a LEMS-induced dysfunction within 15 minutes to 30 minutes after taking their first dose of amifampridine in the morning. Patients were excluded from DAPPER if they had a clinically significant or poorly controlled condition that, in the opinion of the study personnel, might have posed an unacceptable risk to them if they entered into the study. Patients were also excluded if they did not display a sufficiently large response to amifampridine during the baseline observation period; this was defined as a greater than or equal to 27% improvement in 3TUG time compared to the 3TUG time before the first morning dose on 2 consecutive days, or a greater than or equal to 30% improvement after the first morning, afternoon, or evening dose on day 1 plus a greater than or equal to 12% improvement after the first dose of the morning on day 2.

*Baseline Characteristics*

The baseline characteristics were generally balanced between the randomized treatment arms in DAPPER (Table 6). Patients had a mean age of 50.7 (SD = 15.97) and 59.3 (SD = 14.99) in the amifampridine and placebo arms, respectively. Female patients accounted for 71.4% (amifampridine) and 61.1% (placebo) of the population in each arm. One patient in the placebo arm had paraneoplastic syndrome. The mean duration of LEMS diagnosis prior to randomization was 6.7 years in each arm. CMAP characteristics were similar between arms at baseline (Table 7). Baseline use of amifampridine and other LEMS medications were similar between the treatment arms (Table 8). One patient in the amifampridine arm was on only amifampridine at baseline, while all other patients in the amifampridine arm, and all patients in the placebo arm, were on amifampridine in combination with other LEMS medications (e.g., pyridostigmine, immunomodulators, or immunosuppressants).

## Table 6: Summary of Baseline Characteristics

| Characteristics | DAPPER | |
|---|---|---|
| | Continuous amifampridine N = 14 | Taper to placebo N = 18 |
| **Age,** years | | |
| Mean (SD) | 50.7 (15.97) | 59.3 (14.99) |
| Range | 23 to 83 | 28 to 78 |
| **Gender,** n (%) | | |
| Male | 4 (28.6%) | 7 (38.9%) |
| Female | 10 (71.4%) | 11 (61.1%) |
| **Age at time of LEMS diagnosis** (years) | | |
| Mean (SD) | 44.1 (13.79) | 52.7 (14.76) |
| Range | 20 to 63 | 26 to 72 |
| **Time between onset of LEMS symptoms and diagnosis** (years) | | |
| Mean (SD) | 0.9 (0.62) | 2.2 (3.00) |
| Range | 0 to 2 | 0 to 13 |
| **Duration of LEMS diagnosis prior to randomization** (years) | | |
| Mean (SD) | 6.7 (5.70) | 6.7 (6.08) |
| Range | 1.1 to 19.8 | 0.3 to 22.3 |
| **Paraneoplastic syndrome,** n (%) | | |
| Yes | 0 (0.0%) | 1 (5.6%) |
| **Positive P/Q voltage-gated antibodies at screening,** n (%) | | |
| Positive | 12 (85.7%) | 17 (94.4%) |
| **Positive CMAP combined with LEMS at screening,**[a] n (%) | | |
| Yes | 7 (50.0%) | 10 (55.6%) |
| **Indicators of disease severity or complications due to LEMS** | | |
| Ever hospitalized (yes), n (%) | 6 (42.9%) | 7 (38.9%) |
| Ever intubated (yes), n (%) | 1 (7.1%) | 0 (0.0%) |
| Difficulty weaning off ventilator (yes), n (%) | 0 (0.0%) | 0 (0.0%) |

| Characteristics | DAPPER | |
|---|---|---|
| | Continuous amifampridine N = 14 | Taper to placebo N = 18 |
| History of tracheotomy (yes), n (%) | 0 (0.0%) | 0 (0.0%) |
| History of PEG tube placement (yes), n (%) | 0 (0.0%) | 1 (5.6%) |
| Requiring assistive device to walk (yes), n (%) | 2 (14.3%) | 2 (11.1%) |

CMAP = compound muscle action potential; ITT = intention to treat; LEMS = Lambert-Eaton myasthenic syndrome; PEG = percutaneous endoscopic gastrostomy; P/Q = P/Q-type calcium channel; SD = standard deviation.

Note: ITT population.

[a] Positive CMAP combined with LEMS at screening definition was greater than 100% facilitation on pre-dose CMAP after maximal exercise in at least 1 of 3 muscles tested.

Source: Clinical Study Report for JPC 3,4-DAPPER.[13]

## Table 7: Summary of Baseline CMAP Characteristics

| Characteristics | DAPPER | |
|---|---|---|
| | Continuous amifampridine N = 14 | Taper to placebo N = 18 |
| **Day 0 afternoon pre-dose CMAP (mV)** | | |
| ADQ | | |
| N | 5 | 4 |
| Mean (SD) | 4.8 (4.03) | 2.8 (2.10) |
| Range | 0.6 to 9.6 | 0.2 to 5.1 |
| APB | | |
| N | 5 | 11 |
| Mean (SD) | 5.5 (4.90) | 4.0 (2.29) |
| Range | 0.9 to 11.1 | 0.6 to 7.8 |
| EDB | | |
| N | 3 | 2 |
| Mean (SD) | 0.8 (0.41) | 1.7 (1.74) |
| Range | 0.3 to 1.1 | 0.5 to 3.0 |
| **Day 0 afternoon post-dose CMAP (mV)** | | |
| ADQ | | |
| N | 4 | 4 |
| Mean (SD) | 7.1 (4.64) | 4.6 (2.47) |
| Range | 1.1 to 11.0 | 0.9 to 6.5 |
| APB | | |
| N | 4 | 11 |
| Mean (SD) | 6.9 (4.86) | 5.4 (3.46) |
| Range | 2.1 to 13.1 | 0.9 to 10.8 |
| EDB | | |
| N | 3 | 2 |
| Mean (SD) | 1.9 (0.70) | 2.6 (2.19) |
| Range | 1.2 to 2.6 | 1.0 to 4.1 |
| **Optimization CMAP: % facilitation with exercise (%)** | | |
| N | 13 | 17 |
| Mean (SD) | 122.6 (142.5) | 152.4 (217.6) |

| Characteristics | DAPPER | |
|---|---|---|
| | Continuous amifampridine N = 14 | Taper to placebo N = 18 |
| Range | 9.8 to 490 | –0.6 to 850 |

ADQ = abductor digiti quinti muscle; APB = abductor pollicis brevis muscle; CMAP = compound muscle action potential; EDB = extensor digitorum brevis muscle; ITT = intention to treat; mV = millivolts; SD = standard deviation.

Note: ITT population.

Source: Clinical Study Report for JPC 3,4-DAPPER.[13]

## Table 8: Amifampridine and Other LEMS Medication Characteristics at Baseline

| Characteristics | DAPPER | |
|---|---|---|
| | Continuous amifampridine N = 14 | Taper to placebo N = 18 |
| **Duration of amifampridine treatment prior to study entry (years)** | | |
| N | 14 | 18 |
| Mean (SD) | 6.2 (5.30) | 5.5 (4.92) |
| Median (range) | 4.6 (0.7 to 18.9) | 4.3 (0.3 to 18.3) |
| **Duration of current amifampridine treatment regimen (years)** | | |
| N | 14 | 18 |
| Mean (SD) | 2.8 (2.81) | 3.2 (3.55) |
| Median (range) | 2.0 (0.3 to 9.3) | 1.3 (0.3 to 12.0) |
| **Total daily dose of amifampridine at randomization (mg)** | | |
| N | 14 | 18 |
| Mean (SD) | 76.4 (19.46) | 74.7 (22.26) |
| Median (range) | 80.0 (35 to 100) | 80.0 (30 to 100) |
| **Current LEMS treatment regimen,** n (%) | | |
| Amifampridine alone | 1 (7.1%) | 0 (0.0%) |
| Amifampridine + pyridostigmine | 9 (64.3%) | 11 (61.1%) |
| Amifampridine + pyridostigmine + Immunomodulators or immunosuppressants | 2 (14.3%) | 4 (22.2%) |
| Amifampridine + immunomodulators or immunosuppressants | 2 (14.3%) | 3 (16.7%) |
| **Currently on pyridostigmine (yes),** n (%) | 11 (78.6%) | 15 (83.3%) |
| **Total daily dose of pyridostigmine** (mg) | | |
| N | 11 | 15 |
| Mean (SD) | 219.5 (93.02) | 236.0 (138.81) |
| Median (range) | 180 (105 to 360) | 240 (60 to 600) |
| **Historical exposure to prednisone (yes),** n (%) | 7 (50.0%) | 9 (50.0%) |
| **Currently on prednisone (yes),** n (%) | 0 (0.0%) | 0 (0.0%) |
| **Currently on IVIg (yes),** n (%) | 3 (21.4%) | 1 (5.6%) |
| **Time since last IVIg treatment** (days) | | |
| N | 3 | 1 |
| Mean (SD) | 14.2 (9.0) | 12.0 (NA) |
| Median (range) | 10 (8.0 to 24.5) | 12 (12.0 to 12.0) |

ITT = intention to treat; IVIg = intravenous immunoglobulin; LEMS = Lambert-Eaton myasthenic syndrome; NA = not applicable; SD = standard deviation.

Note: ITT population.

Source: Clinical Study Report for JPC 3,4-DAPPER.[13]

## Interventions

Patients eligible for enrolment in DAPPER were centrally randomized in a 1:1 ratio to continue their current treatment regimen (group A, continuous amifampridine) or to withdraw from amifampridine (group B, taper to placebo) for up to 3 and a half days.

Patients randomized to the continuous-amifampridine arm received 4 tablets delivering the same amounts of amifampridine they were accustomed to taking at home. For patients randomized to the taper-to-placebo arm, the first taper after randomization was to 90% of their usual dose with the last dose of day 2. Each subsequent dose decreased so that they reached 50% of their usual dose at the end of day 3, 25% at the end of day 4, and 0% (i.e., placebo) in the middle of day 5. Placebo continued until the first dose of the morning on day 6, when they returned to their usual fully active morning dose.

Rescue (i.e., urgent return to dose of amifampridine at baseline) was considered in the following situations: new dysphagia; a drop in pulse oximetry of 5% from baseline; or a decrease in pulse oximetry to less than 90% with an accompanying description of shortness of breath. Patients could advance to stage 3 (restore baseline amifampridine) if either of the following criteria were met: inability to rise from a chair, even with assistance, after 2 efforts about 1 hour apart; or inability to get out of bed, even with assistance, after 2 efforts about 1 hour apart.

Blinding of the patients, investigator, site personnel, and sponsor personnel was maintained using identical tablets and centralized clinical supply packaging.

Patients who had received treatment with pyridostigmine, immunomodulators or immunosuppressants, or steroids as part of their pre-study treatment regimen were to be continued on their usual dosages. The use of aminopyridines (e.g., 4-AP) or guanidine was prohibited. The use of IVIg and plasmapheresis were not permitted during the inpatient portion DAPPER. No new LEMS treatments (started within the past 3 months) were permitted. There were no other restrictions on concomitant medications.

## Outcomes

A list of efficacy end points identified in the CADTH review protocol that were assessed in the clinical trial included in this review is provided in Table 9. These end points are further summarized in the discussion that follows. A detailed discussion and critical appraisal of the outcome measures is provided in Appendix 4.

### Table 9: Summary of Outcomes of Interest Identified in the CADTH Review Protocol

| Outcome measure | DAPPER |
|---|---|
| Categorization of the degree of change in the 3TUG test score upon withdrawal of active medication (> 30% deterioration in 3TUG time) | Primary |
| W-SAS | Secondary |
| CMAP | Other |
| LEFS | Exploratory |
| LEMS-related ADLs | Exploratory |

3TUG = Triple-Timed Up-and-Go; ADLs = activities of daily living; CMAP = compound muscle action potential; LEFS = Lower Extremity Functional Scale; LEMS = Lambert-Eaton myasthenic syndrome; W-SAS = self-assessment of LEMS-related weakness.

*Disability Progression*

Disability progression was assessed in DAPPER using the 3TUG test, W-SAS, CMAP, and LEFS.

The 3TUG test is a non-invasive measure of disease severity in patients with LEMS. It consists of 3 consecutive laps where the patient rises from a straight-backed chair, walks 3 metres, and returns to the chair. The 3TUG time is the average of the 3 lap times. Higher 3TUG scores represent greater impairment. In DAPPER, the 3TUG score was assessed according to the following 7 categories from A to G: A: greater than 30% faster; B: 30% slower to 30% faster; C: greater than 30% to 50% slower; D: greater than 50% to 100% slower; E: greater than100% to 200% slower; F: greater than 200% slower; G: cannot perform 3TUG. In an assessment of validity, the a priori acceptable range was a difference of less than 20% in 3TUG times and a coverage probability (CP) greater than or equal to 0.90 confirmed agreement as determined by neuromuscular physicians. In an assessment of 12 patients with LEMS, the CP was 0.92. Inter-rater reliability testing showed that an average difference in 3TUG times measured did not exceed 20% for any of the pairs, resulting in a CP of 1.0 in all groups assessed.[11]

In DAPPER, the primary efficacy end point was the categorization of the degree of change in the 3TUG test score (last observation at the theoretical "peak drug effect'" i.e., 2 hours post-dose) upon withdrawal of the active medication (stage 2) when compared with the time-matched average of the 3TUG assessments during stage 1. In DAPPER, this was categorized as a deterioration of greater than 30% in 3TUG time, which is clinically relevant based on the literature and input from the clinical experts consulted for the CADTH review.[11] The 3TUG was assessed by an onsite assessor and through recording by a blinded assessor. The recorded, blinded assessment was used for the primary efficacy assessment.

The secondary efficacy end point in DAPPER was the W-SAS, a single-item, global self-assessment scale for LEMS-related weakness. The W-SAS was assessed at the end of stage 2 as compared to the baseline. The W-SAS assesses weakness using a 7-category scale with numerical values where weakness is ranked along a continuum from "much much weaker" (–3) to "much much stronger" (+3). No studies assessing the validity, reliability, or MID of the W-SAS were identified for patients with LEMS.

CMAP was assessed as an "other" end point in DAPPER. CMAP measures the response of individual muscles to nerve stimulation. CMAPs were assessed at the trough before the first dose of the day and at the theoretical peak (2 hours after the first dose) using 1 nerve-muscle combination identified during the optimization procedure. CMAP optimization on the day of admission was used to determine the most responsive nerve-muscle combination. CMAP comparisons between stages were time-specific. A decrease between the time-matched CMAPs in stages 1 and 2 was considered confirmatory of deterioration in 3TUG.

The LEFS is a 20-item, patient-reported outcome measure commonly used to assess mobility in patients with orthopedic conditions. The scale is 1 page; items are rated on a 5-point scale from 0 (extreme difficulty or unable to perform activity) to 4 (no difficulty). The total possible score is 80 and indicates a high functional level. Construct validity was established in a population with lower-extremity musculoskeletal dysfunction by comparison with the Short Form (36) Health Survey (SF-36) physical function subscale ($r$ = 0.80), SF-36 physical component summary score ($r$ = 0.64), and SF-36 mental component summary score ($r$ = 0.30).[22] No MID for the LEFS was identified for patients with LEMS. A MID of 9

points has been identified for the population with lower-extremity musculoskeletal dysfunction.

### *Activities of Daily Living*

LEMS-related ADLs were used as a functional measurement in DAPPER and assessed as a 6-item patient-reported outcome measure. The outcomes were scored from 1 (worst) to 4 (best) and included toileting or bathing, dressing, eating and drinking, sit-to-stand, grooming, and bed mobility. No studies assessing validity, reliability, or the MID of LEMS-related ADLs were identified for patients with LEMS.

### *Other*

The following CADTH protocol-specified outcomes were not assessed in DAPPER: LEMS-related symptoms, HRQoL, and productivity (e.g., attending school or work).

## Statistical Analysis

In DAPPER, an estimated 10 patients per treatment arm were required to achieve at least 80% power with an alpha of 0.5. It was assumed that 10% of patients in the continuous-amifampridine arm and 80% of those in the taper-to-placebo arm would meet the primary efficacy end point (deterioration in 3TUG test results of 30% or more).

The primary efficacy end point for deterioration in 3TUG results of 30% or more compared the 2 treatment arms using Fisher's exact test after determining the response rate for outcomes C through G combined for each arm. The individual 7 categories (A though G) were summarized and compared by treatment arms using the Cochran-Mantel-Haenszel test with modified Ridit scores derived from category rankings. The correlation between blinded 3TUG times and onsite 3TUG times was analyzed using Pearson's method.

The secondary efficacy end point for observation of W-SAS during stage 2 using a categorical scale was compared with the baseline score. Treatment arms were compared using a t-test. The treatment arms were also compared using the Cochran-Mantel-Haenszel test with modified Ridit scores derived from category rankings.

No formal statistical hypothesis testing was performed for "other" outcomes or exploratory outcomes. A statistical testing hierarchy was not used for the assessment of any outcomes in DAPPER. No sensitivity analyses were performed. No subgroup analyses (identified in the CADTH protocol) were performed. Statistical methods were not used to impute missing data. Rescued patients, early advanced patients, and patients who withdrew early from stage 2 were categorized for analysis of the 3TUG test according to the last observation at theoretical "peak drug effect" during stage 2 carried forward. For the W-SAS assessment, the last observation during stage 2 served as the secondary end point.

### *Analysis Populations*

- The efficacy population consisted of all patients who were randomized, took any of the study regimen, and had at least 1 post-baseline 3TUG test result at the theoretical "peak drug effect" (i.e., 2 hours post-dose). The primary efficacy analysis was performed using the efficacy population.
- The ITT population consisted of all randomized patients, including those who were replaced due to withdrawal of consent after randomization but prior to admission into the clinical research unit.

- The per-protocol (PP) population consisted of all patients who completed the clinical trial according to the protocol.
- The safety population consisted of all randomized patients who received any amount of the study treatment regimen and were evaluated for safety.

## Results

### Patient Disposition

In DAPPER, 52 patients were screened. Among them, 14 were randomized to treatment with continuous amifampridine and 18 were randomized to taper to placebo. The most common reason for screen failure was related to insufficient response to 3TUG during stage 1 (n = 18).

Two patients (14.3%) in the continuous-amifampridine arm had early entry into stage 3 of the trial; this was attributed to new dysphagia. Eight patients (44.4%) in the taper-to-placebo arm had early entry into stage 3 of the trial; this was attributed to new dysphagia for 5 patients (27.8%). No patients discontinued from the study. The ITT population was identical to the (primary) efficacy population.

## Table 10: Patient Disposition

| | DAPPER | |
|---|---|---|
| | **Continuous amifampridine** | **Taper to placebo** |
| **Screened, N** | 52 | |
| **Randomized,[a] N (%)** | 14 (100%) | 18 (100%) |
| **Completed stage 2, N (%)** | 14 (100%) | 18 (100%) |
| **Early entry to stage 3** | 2 (14.3%) | 8 (44.4%) |
| Rescued due to: | | |
| New dysphagia | 2 (14.3%) | 5 (27.8%) |
| Drop in pulse/ox[b] | 0 (0.0%) | 1 (5.6%) |
| Advanced due to: | | |
| Inability to rise from a chair[c] | 0 (0.0%) | 1 (5.6%) |
| Inability to get out of bed[d] | 0 (0.0%) | 0 (0.0%) |
| Patient request for active medication | 0 (0.0%) | 1 (5.6%) |
| **Discontinued from study, N (%)** | 0 | 0 |
| **ITT, N** | 14 (100.0%) | 18 (100.0%) |
| **PP, N** | 13 (92.9%) | 18 (100.0%) |
| **Efficacy, N** | 14 (100.0%) | 18 (100.0%) |
| **Safety, N** | 14 (100.0%) | 18 (100.0%) |

ITT = intention to treat; PP = per protocol; pulse/ox = pulse oximetry.

[a] Completed stage 1.

[b] Drop in pulse/ox of 5% from baseline or a decrease to less than 90% with accompanying shortness of breath.

[c] Inability to rise from a chair, even with assistance, after 2 efforts 1 hour apart.

[d] Inability to get out of bed, even with assistance, after 2 efforts 1 hour apart.

Source: Clinical Study Report for JPC 3,4-DAPPER.[13]

### Exposure to Study Treatments

In DAPPER, 32 patients were randomized and received baseline treatment with amifampridine at daily doses ranging from
30 mg/day to 100 mg/day. The average amifampridine dose at baseline was 76.4 mg/day in the continuous-amifampridine arm and 74.7 mg/day and taper-to-placebo arm. Amifampridine administration is presented by day in Table 11.

The majority of patients in the DAPPER study were taking concomitant LEMS-related medication in addition to amifampridine. Use of non-amifampridine LEMS-related concomitant medication was similar for patients randomized to continuous amifampridine (78.6%) and taper to placebo (72.2%) (Table 12).

## Table 11: Amifampridine Administration and Extent of Exposure (Safety Population)

| Study day | DAPPER | | | |
|---|---|---|---|---|
| | Continuous amifampridine N = 14 | | Taper to placebo N = 18 | |
| | Dose taken (mg) | Percentage (%) | Dose taken (mg) | Percentage (%) |
| **Day 1,** n (%) | 14 | 14 | 18 | 18 |
| Mean (SD) | 76.4 (19.46) | 100.0 (0.0) | 74.7 (22.26) | 100.0 (0.0) |
| Range | 35.0 to 100.0 | 100.0 to 100.0 | 30.0 to 100.0 | 100.0 to 100.0 |
| **Day 2,** n (%) | 14 | 14 | 18 | 18 |
| Mean (SD) | 76.4 (19.46) | 100.0 (0.0) | 73.3 (22.02) | 98.0 (0.73) |
| Range | 35.0 to 100.0 | 100.0 to 100.0 | 29.0 to 99.0 | 96.7 to 99.0 |
| **Day 3,** n (%) | 14 | 14 | 18 | 18 |
| Mean (SD) | 76.4 (19.46) | 100.0 (0.0) | 49.9 (14.82) | 67.0 (2.13) |
| Range | 35.0 to 100.0 | 100.0 to 100.0 | 21.0 to 68.5 | 63.3 to 70.0 |
| **Day 4,** n (%) | 14 | 14 | 18 | 18 |
| Mean (SD) | 72.1 (24.55) | 100.0 (0.0) | 23.2 (6.88) | 32.9 (3.69) |
| Range | 20.0 to 100.0 | 100.0 to 100.0 | 11.5 to 32.5 | 28.8 to 40.0 |
| **Day 5,** n (%) | 12 | 12 | 13 | 13 |
| Mean (SD) | 78.3 (19.46) | 100.0 (0.0) | 3.4 (3.19) | 5.9 (3.75) |
| Range | 35.0 to 100.0 | 100.0 to 100.0 | 1.0 to 13.5 | 2.5 to 13.5 |
| **Day 6,**[a] n (%) | 12 | 12 | 10 | 10 |
| Mean (SD) | 27.5 (9.89) | 100.0 (0.0) | 23.0 (10.59) | 100.0 (0.0) |
| Range | 10.0 to 40.0 | 100.0 to 100.0 | 10.0 to 40.0 | 100.0 to 100.0 |

SD = standard deviation.

Note: Percentage is based on percentage of baseline dose. Dose taken is total daily dose from days 1 through 5 and a partial day's (morning) dose on day 6 or on the day of rescue or early advance to stage 3, if prior to day 6. The decrease in the number of patients from 14 to 12 on days 5 and 6 in the continuous-amifampridine group reflects the 2 patients in this group who experienced new dysphagia and were rescued early on day 4.

[a] Day 6 “dose taken” values are based on the morning dose only and represent a partial day’s dose.

Source: Clinical Study Report for JPC 3,4-DAPPER.[13]

## Table 12: Summary of LEMS-Related Concomitant Medications (Safety Population)

| Characteristics | DAPPER | |
|---|---|---|
| | Continuous amifampridine N = 14 | Taper to placebo N = 18 |
| **Taking at least 1 LEMS-related concomitant medication during the study,** n (%) | 11 (78.6%) | 13 (72.2%) |
| **Immunosuppressants,** n (%) | 2 (14.3%) | 7 (38.9%) |
| Imuran or azathioprine | 0 (0.0%) | 3 (16.7%) |
| Cellcept or mycophenolate/mycophenolate mofetil | 2 (14.3%) | 4 (22.2%) |
| **Other nervous system drugs,** n (%) | 10 (71.4%) | 10 (55.6%) |
| Mestinon or pyridostigmine formulations | 10 (71.4%) | 10 (55.6%) |

LEMS = Lambert-Eaton myasthenic syndrome.

Note: The table includes only medications taken during the inpatient study and excludes LEMS medications taken either before admission to the inpatient research unit or during the follow-up phase of the study. (In particular, 4 patients — 1 in the taper-to-placebo group and 3 in the group receiving continuous amifampridine — were on intermittent intravenous immunoglobulin every 3 weeks as a stable component of their LEMS-related therapeutic regimens, and treatment was given both before admission and after they were discharged from the research unit.)

Source: Clinical Study Report for JPC 3,4-DAPPER.[13]

### Efficacy

Only the efficacy outcomes and analyses of the subgroups identified in the CADTH review protocol are reported here.

#### *Disability Progression*

**Triple-Timed Up-and-Go Test**

None of the patients (0%) in the continuous-amifampridine arm had a deterioration of 30% or greater in the final (blinded) 3TUG test after withdrawal of the study drug (stage 2), compared to 72.2% of patients in the taper-to-placebo arm (P < 0.0001) (Table 13). The treatment effect based on the 3TUG test was statistically significant in favour of continuous amifampridine. The primary efficacy results in the efficacy population were consistent with the results of the ITT and PP population. The Pearson correlation coefficient was 0.9192 for the comparison between blinded 3TUG and onsite 3TUG assessments. Kaplan-Meier plots for the time to 30% or greater deterioration in post-dose 3TUG are presented in Appendix 3, Figure 8.

None of the patients treated with continuous amifampridine reached the threshold of 50% or greater deterioration in 3TUG test results, compared to 44.4% of patients in the taper-to-placebo arm (P = 0.0044) (Table 13).

Table 13 presents the categorical degree of change for each treatment arm using the 3TUG test after withdrawal of the study drug (stage 2). No patients in the continuous-amifampridine arm were slower than 30% deterioration (categories C to G).

Figure 4 presents the percentage change from time-matched baseline in 3TUG at 2 hours after dosing versus time. A difference between treatment groups is observed for the 2-hour post-dose 3TUG change from baseline from the day 4 evening dose (P < 0.05) to the day 5 evening dose in favour of treatment with continuous amifampridine (P < 0.001).

## Table 13: Deterioration in 3TUG (Efficacy Population)

| | DAPPER | |
|---|---|---|
| | Continuous amifampridine N = 14 | Taper to placebo N = 18 |
| **Category of change in 3TUG (> 30% deterioration)[a,b]** | | |
| Category A to category B (no change or faster) | 14 (100.0%) | 5 (27.8%) |
| Category C to category G (> 30% slower) | 0 (0.0%) | 13 (72.2%) |
| P value | < 0.0001 | |
| **Category of change in 3TUG (> 50% deterioration)[a,b]** | | |
| Category A to category C (no change or faster) | 14 (100.0%) | 10 (55.6%) |
| Category D to category G (> 50% slower) | 0 (0.0%) | 8 (44.4%) |
| P value | 0.0044 | |
| **Category of change in 3TUG[c]** | | |
| A: > 30% faster | 0 (0.0%) | 0 (0.0%) |
| B: No change | 14 (100%) | 5 (27.8%) |
| C: > 30% to 50% slower | 0 (0.0%) | 5 (27.8%) |
| D: > 50% to 100% slower | 0 (0.0%) | 5 (27.8%) |
| E: > 100% to 200% slower | 0 (0.0%) | 1 (5.6%) |
| F: > 200% slower | 0 (0.0%) | 2 (11.1%) |
| G: Cannot perform TUG | 0 (0.0%) | 0 (0.0%) |
| P value | 0.0008 | |

3TUG = Triple-Timed Up-and-Go; TUG = Timed Up-and-Go.

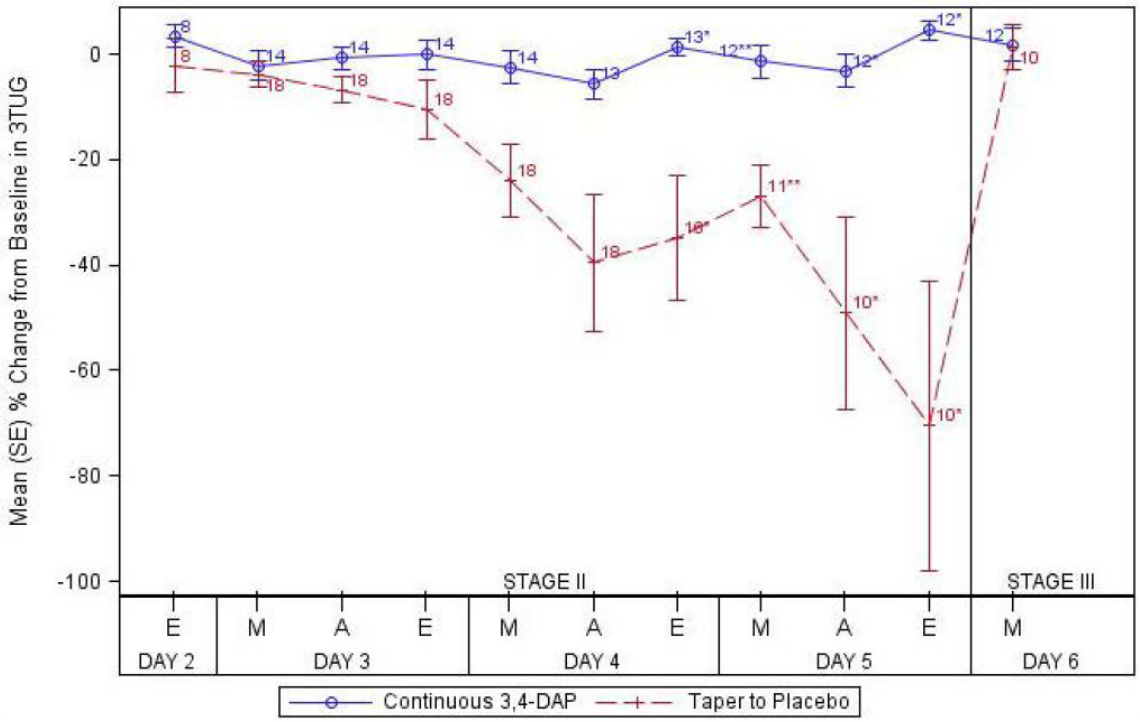
[a] Definition of the categories: A: greater than 30% faster; B: 30% slower to 30% faster; C: greater than 30% to 50% slower; D: greater than 50% to 100% slower; E: greater than 100% to 200% slower; F: greater than 200% slower; G: cannot perform 3TUG.

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

[c] P value based on Cochran-Mantel-Haenszel test.

Source: Clinical Study Report for JPC 3,4-DAPPER.[13]

## Figure 4: Mean (SE) Percentage Change From Baseline in 3TUG at 2 Hours After Dosing Versus Time by Treatment Groups




3,4-DAP = 3,4-diaminopyridine; 3TUG = Triple-Timed Up-and-Go; A = afternoon; ANCOVA = analysis of covariance; E = evening; M = morning; SE = standard error.

Note: Efficacy population. The P value is based on the 1-way ANCOVA model, with the baseline 3TUGs as the covariate.

* P value < 0.05.

** P value < 0.01.

*** P value < 0.001.

Source: Clinical Study Report for JPC 3,4-DAPPER.[13]

### *Self-Assessment of LEMS-Related Weakness*

The mean W-SAS final score was greater in the continuous-amifampridine arm than in the taper-to-placebo arm (–0.2 [SD = 1.19] versus –2.4 [SD = 0.85], respectively; P < 0.0001) (Table 14). The treatment effect based on W-SAS favoured continuous amifampridine. The results for the W-SAS by category are presented in Table 14.

## Table 14: W-SAS (Efficacy Population)

| | DAPPER | |
|---|---|---|
| | Continuous amifampridine N = 14 | Taper to placebo N = 18 |
| **Final W-SAS score[a,b]** | | |
| n | 14 | 18 |
| Mean (SD) | –0.2 (1.19) | –2.4 (0.85) |
| Median (range) | 0.0 (–3.0 to 2.0) | –3.0 (–3.0 to 0.0) |
| P value | < 0.0001 | |
| **Final W-SAS category,[a,b] n (%)** | | |
| Much weaker (–3) | 1 (7.1%) | 10 (55.6%) |
| Much weaker (–2) | 1 (7.1%) | 6 (33.3%) |
| Somewhat weaker (–1) | 1 (7.1%) | 1 (5.6%) |
| About the same (0) | 9 (64.3%) | 1 (5.6%) |
| Somewhat stronger (1) | 1 (7.1%) | 0 (0.0%) |
| Much stronger (2) | 1 (7.1%) | 0 (0.0%) |
| Much stronger (3) | 0 (0.0%) | 0 (0.0%) |
| P value | < 0.0001 | |

SD = standard deviation; W-SAS = self-assessment of LEMS-related weakness.

[a] The last observation during stage 2 served as the final W-SAS.

[b] The P value is based on the Cochran-Mantel-Haenszel test for categorical data and on the t-test for continuous data.

Source: Clinical Study Report for JPC 3,4-DAPPER.[13]

### Compound Muscle Action Potential

The mean (SD) CMAP assessment based on the change from baseline to the last available post-dose during stage 2 for all muscle types was –4.6% (28.95) for patients treated with continuous amifampridine and –48.5% (19.78) in the taper-to-placebo arm (Table 15). The results for the individual nerve-muscle pairs (abductor digiti quinti, abductor pollicis brevis muscle, and extensor digitorum brevis muscle) are presented in Table 15. The CMAP assessments made by blinded assessors are reported in Appendix 3, Table 29.

## Table 15: Compound Muscle Action Potential (Efficacy Population)

| | DAPPER | | | |
|---|---|---|---|---|
| | Continuous amifampridine N = 14 | | Taper to placebo N = 18 | |
| **Muscle statistics** | **Measurement (mV)** | **% change from baseline [a]** | **Measurement (mV)** | **% change from baseline [a]** |
| All muscle types | | | | |
| n | 14 | 14 | 18 | 18 |
| Mean (SD) | 5.4 (4.05) | –4.6 (28.95) | 2.4 (1.77) | –48.5 (19.78) |
| Median (range) | 5.0 (0.9 to 11.2) | –9.3 (–66.5 to 66.9) | 2.3 (0.2 to 5.2) | –49.9 (–80.9 to –7.9) |
| ADQ | | | | |
| n | 6 | 6 | 4 | 4 |
| Mean (SD) | 6.0 (4.08) | 3.9 (31.91) | 2.2 (1.96) | –43.2 (31.58) |
| Median (range) | 7.1 (0.9 to 11.2) | –8.3 (–18.2 to 66.9) | 1.8 (0.2 to 4.8) | –47.0 (–70.8 to –7.9) |
| APB | | | | |
| n | 5 | 5 | 12 | 12 |
| Mean (SD) | 6.9 (4.27) | 0.4 (17.97) | 2.7 (1.81) | –50.2 (17.68) |
| Median (range) | 8.4 (2.1 to 10.8) | –3.0 (–19.8 to 27.3) | 2.6 (0.3 to 5.2) | –49.9 (–80.9 to –28.0) |
| EDB | | | | |
| n | 3 | 3 | 2 | 2 |
| Mean (SD) | 1.8 (1.38) | –30.1 (31.66) | 1.3 (1.34) | –48.9 (8.59) |
| Median (range) | 1.1 (0.9 to 3.4) | –14.8 (–66.5 to –9.0) | 1.3 (0.3 to 2.2) | –48.9 (–55.0 to –42.9) |

ADQ = abductor digiti quinti muscle; APB = abductor pollicis brevis muscle; EDB = extensor digitorum brevis muscle; mV = millivolts; SD = standard deviation.

Note: Last available post-dose CMAP during stage 2. A positive percentage change is an improvement in CMAP, and a negative percentage change is a deterioration in CMAP.

[a] Baseline is the average of time-matched observations at post-dose on days 1 and 2 in stage 1.

Source: Clinical Study Report for JPC 3,4-DAPPER.[13]

### Lower Extremity Functional Scale

The mean (SD) change from baseline in LEFS score was –2.6% (10.03) in the continuous-amifampridine arm and –24.8% (16.43) in the taper-to-placebo arm (Table 16). Results for the LEFS at 4 weeks post-discharge are presented in Table 16.

## Table 16: Lower Extremity Functional Scale Scores (Efficacy Population)

| | DAPPER | | | |
|---|---|---|---|---|
| | Continuous amifampridine N = 14 | | Taper to placebo N = 18 | |
| | Measurement | % change from baseline[a] | Measurement | % change from baseline[a] |
| Baseline [a] | | | | |
| n | 14 | | 18 | |
| Mean (SD) | 42.3 (17.17) | | 40.7 (14.84) | |
| Median (range) | 37.5 (20.0 to 79.0) | | 41.5 (15.0 to 70.0) | |
| End of stage 2 | | | | |
| n | 14 | 14 | 17 | 17 |
| Mean (SD) | 39.6 (19.70) | –2.6 (10.03) | 17.1 (15.38) | –24.8 (16.43) |
| Median (range) | 39.0 (8.0 to 79.0) | –1.5 (–24.0 to 10.0) | 10.0 (0.0 to 54.0) | –27.0 (–60.0 to 0.0) |
| 4 weeks post-discharge | | | | |
| n | 14 | 14 | 17 | 17 |
| Mean (SD) | 41.1 (15.68) | –1.1 (10.41) | 40.2 (16.68) | –0.8 (14.08) |
| Median (range) | 37.5 (20.0 to 66.0) | 2.0 (–23.0 to 12.0) | 43.0 (15.0 to 74.0) | 2.0 (–44.0 to 20.0) |

SD = standard deviation.

[a] Baseline is defined as the last available assessment prior to stage 2 (obtained on day 0).

Source: Clinical Study Report for JPC 3,4-DAPPER.[13]

### LEMS-Related Activities of Daily Living

LEMS-related ADLs for toileting and bathing, dressing, eating and drinking, sit-to-stand, grooming, and bed mobility at baseline and day 5 are reported in Table 17.

## Table 17: LEMS-Related Activities of Daily Living Scores (Efficacy Population)

| | DAPPER | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Continuous amifampridine N = 14 | | | | | Taper to placebo N = 18 | | | | |
| | Baseline, n (%)[a] | | | | | | | | | |
| **Toileting and bathing[b]** | Level 1 | Level 2 | Level 3 | Level 4 | Total | Level 1 | Level 2 | Level 3 | Level 4 | Total |
| Day 5, n (%) | | | | | | | | | | |
| Level 1 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Level 2 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (5.6%) | 1 (5.6%) |
| Level 3 | 0 (0.0%) | 0 (0.0%) | 1 (7.1%) | 0 (0.0%) | 1 (7.1%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (5.6%) | 1 (5.6%) |
| Level 4 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 11 (78.6%) | 11 (78.6%) | 0 (0.0%) | 0 (0.0%) | 1 (5.6%) | 7 (38.9%) | 8 (44.4%) |
| Total | 0 (0.0%) | 0 (0.0%) | 1 (7.1%) | 11 (78.6%) | 12 (85.7%) | 0 (0.0%) | 0 (0.0%) | 1 (5.6%) | 9 (50.0%) | 10 (55.6%) |
| **Dressing[c]** | | | | | | | | | | |
| Day 5, n (%) | | | | | | | | | | |
| Level 1 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Level 2 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (5.6 %) | 1 (5.6 %) |
| Level 3 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Level 4 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 12 (85.7%) | 12 (85.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 9 (50.0%) | 9 (50.0%) |
| Total | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 12 (85.7%) | 12 (85.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 10 (55.6%) | 10 (55.6%) |
| **Eating and drinking[d]** | | | | | | | | | | |
| Day 5, n (%) | | | | | | | | | | |
| Level 1 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Level 2 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Level 3 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 2 (11.1%) | 2 (11.1%) |
| Level 4 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 12 (85.7%) | 12 (85.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 8 (44.4%) | 8 (44.4%) |
| Total | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 12 (85.7%) | 12 (85.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 10 (55.6%) | 10 (55.6%) |
| **Sit-to-stand[e]** | | | | | | | | | | |
| Day 5, n (%) | | | | | | | | | | |
| Level 1 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Level 2 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (5.6%) | 1 (5.6%) |
| Level 3 | 0 (0.0%) | 0 (0.0%) | 6 (42.9%) | 0 (0.0%) | 6 (42.9%) | 0 (0.0%) | 0 (0.0%) | 3 (16.7%) | 4 (22.2%) | 7 (38.9%) |

| | DAPPER | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Continuous amifampridine N = 14 | | | | | Taper to placebo N = 18 | | | | |
| Level 4 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 6 (42.9%) | 6 (42.9%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 2 (11.1%) | 2 (11.1%) |
| Total | 0 (0.0%) | 0 (0.0%) | 6 (42.9%) | 6 (42.9%) | 12 (85.7%) | 0 (0.0%) | 0 (0.0%) | 3 (16.7%) | 7 (38.9%) | 10 (55.6%) |
| **Grooming[f]** | | | | | | | | | | |
| Day 5, n (%) | | | | | | | | | | |
| Level 1 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Level 2 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (5.6%) | 1 (5.6%) |
| Level 3 | 0 (0.0%) | 0 (0.0%) | 1 (7.1%) | 0 (0.0%) | 1 (7.1%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (5.6%) | 1 (5.6%) |
| Level 4 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 11 (78.6%) | 11 (78.6%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 8 (44.4%) | 8 (44.4%) |
| Total | 0 (0.0%) | 0 (0.0%) | 1 (7.1%) | 11 (78.6%) | 12 (85.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 10 (55.6%) | 10 (55.6%) |
| **Bed mobility[g]** | | | | | | | | | | |
| Day 5, n (%) | | | | | | | | | | |
| Level 1 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Level 2 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Level 3 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (5.6%) | 1 (5.6%) |
| Level 4 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 12 (85.7%) | 12 (85.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 9 (50.0%) | 9 (50.0%) |
| Total | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 12 (85.7%) | 12 (85.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 10 (55.6%) | 10 (55.6%) |

[a] Baseline is defined as the worst result during day 0 and day 1.

[b] Level 1: cannot get to bathroom or get out of bed to go to toilet or use bedside commode; level 2: cannot get to bathroom to bathe, but able to get out of bed to use bedside commode; level 3: independent, but requires assistive device(s) for bathing and/or toileting in bathroom; level 4: independent with bathing and toileting; no need for assistive device(s) in bathroom.

[c] Level 1: totally dependent in dressing; level 2: requires assistance in donning shirt or robe and pants or skirt and/or socks and/or shoes; level 3: able to put on shirt or robe independently, but requires assistance to put on pants or skirt and/or socks and/or shoes; level 4: independent in dressing.

[d] Level 1: unable to eat or drink, even with assistance; level 2: requires full assistance with eating and drinking; level 3: unable to cut food or open food containers, but able to feed self once food has been cut or opened, and/or eating and drinking are noticeably slowed; level 4: independent in eating and drinking.

[e] Level 1: unable to stand from seated position; level 2: sit-to-stand with assistance of 1 or more people; level 3: sit-to-stand using arms for added lift (with or without leaning forward or rocking); level 4: independent; can perform sit-to-stand without using arms.

[f] Level 1: cannot raise arm(s) to brush teeth or brush or comb hair or shave; level 2: can raise arm(s) to mouth and/or face and/or crown to simulate grooming, but cannot groom; level 3: can raise arm(s) to brush teeth or brush or comb hair or shave, but cannot complete grooming and/or grooming is noticeably slowed or prolonged; level 4: independent in grooming.

[g] Level 1: bedbound; cannot roll over in bed; level 2: bedbound; can roll from side to side at least once; level 3: bedbound; can sit up without assistance but cannot move legs to dangle feet; level 4: can sit up in bed, dangle, and place feet on ground.

Source: Clinical Study Report for JPC 3,4-DAPPER.[13]

**Other**

The following CADTH protocol-specified outcomes were not assessed in DAPPER: LEMS-related symptoms, HRQoL, and productivity (e.g., attend school or work).

## Harms

Only those harms identified in the review protocol are reported here. See Table 18 and Table 19 for detailed harms data.

### *Adverse Events*

In DAPPER, AEs excluding LEMS-related signs and symptoms occurred in 5 patients (35.7%) in the continuous-amifampridine arm and in 12 patients (66.7%) in the taper-to-placebo arm. The most common AEs were abdominal discomfort and respiratory tract infection, each of which occurred in 2 patients (11.1%) in the taper-to-placebo arm. Treatment-emergent AEs, excluding LEMS-related signs and symptoms, are reported in Table 18.

AEs attributed to LEMS-related signs and symptoms occurred in 2 patients (14.3%) in the continuous-amifampridine arm and in 6 patients (33.3%) in the taper-to-placebo arm. The most common AEs were decreased oxygen saturation (n = 3, 16.7%), muscle spasms (n = 2, 11.1%), and nausea (n = 2, 11.1%), each of which occurred in patients in the taper-to-placebo arm. Treatment-emergent AEs attributed to LEMS-related signs are reported in Table 19.

### *Serious Adverse Events*

In DAPPER, no patients treated with continuous amifampridine experienced an SAE excluding LEMS-related signs and symptoms. One patient (5.6%) in the taper-to-placebo arm experienced an SAE of severe pneumonia (Table 18).

No patients in either treatment arm experienced an SAE attributed to LEMS-related signs and symptoms (Table 19).

### *Withdrawals Due to Adverse Events*

No patients in either treatment group in DAPPER stopped treatment due to AEs excluding LEMS-related signs and symptoms (Table 18).

No patients in the continuous-amifampridine arm withdrew from treatment due to AEs attributed to LEMS-related signs and symptoms. Two patients in the taper-to-placebo arm withdrew from treatment due to AEs attributed to LEMS-related signs and symptoms: decreased oxygen saturation (5.6%) and anxiety (5.6%).

### *Mortality*

No deaths were reported during DAPPER.

One patient died after more than 1 year following completion of the DAPPER.

### *Notable Harms*

Notable harms identified in the protocol for this review included: clinically significant electrocardiogram, paresthesia, and seizures.

None of the patients in the continuous-amifampridine arm and 1 patient (5.6%) in the taper-to-placebo arm experienced prolonged QT assessed through electrocardiogram. None of the patients in the continuous-amifampridine arm and 1 patient (5.6%) in the taper-to-placebo arm experienced paresthesia. Seizures were not reported in DAPPER.

## Table 18: Summary of Harms Excluding LEMS-Related Signs and Symptoms (Safety Population)

| | DAPPER | |
|---|---|---|
| | Continuous amifampridine N = 14 | Taper to placebo N = 18 |
| **Patients with ≥ 1 adverse event** | | |
| n (%) | 5 (35.7%) | 12 (66.7%) |
| Most common events,[a] n (%) | | |
| Abdominal discomfort | 0 | 2 (11.1%) |
| Respiratory tract infection | 0 | 2 (11.1%) |
| **Patients with ≥ 1 SAE** | | |
| n (%) | 0 | 1 (5.6%) |
| Severe pneumonia | 0 | 1 (5.6%) |
| **Patients who stopped treatment due to adverse events** | | |
| n (%) | 0 | 0 |
| **Deaths** | | |
| n (%) | 0 | 0 |
| **Notable harms, n (%)** | | |
| Clinically significant electrocardiogram | 0 | 0 |
| Electrocardiogram QT prolonged | 0 | 1 (5.6%) |
| Paresthesia | 0 | 1 (5.6%) |
| Seizures | NR | NR |

LEMS = Lambert-Eaton myasthenic syndrome; NR = not reported; SAE = serious adverse event.

[a] Frequency greater than 1 patient per arm.

Source: Clinical Study Report for JPC 3,4-DAPPER.[13]

## Table 19: Summary of LEMS-Related Signs and Symptoms (Safety Population)

| | DAPPER | |
|---|---|---|
| | Continuous amifampridine N = 14 | Taper to placebo N = 18 |
| **Patients with ≥ 1 adverse event** | | |
| n (%) | 2 (14.3%) | 6 (33.3%) |
| Most common events,[a] n (%) | | |
| Oxygen saturation decreased | 0 | 3 (16.7%) |
| Muscle spasms | 0 | 2 (11.1%) |
| Nausea | 0 | 2 (11.1%) |
| **Patients with ≥ 1 SAE** | | |
| n (%) | 0 | 0 |

| | DAPPER | |
|---|---|---|
| | Continuous amifampridine N = 14 | Taper to placebo N = 18 |
| **Patients who stopped treatment due to adverse events** | | |
| n (%) | 0 | 2 (11.1%) |
| Oxygen saturation decreased | 0 | 1 (5.6%) |
| Anxiety | 0 | 1 (5.6%) |
| **Deaths** | | |
| n (%) | 0 | 0 |
| **Notable harms, n (%)** | | |
| Clinically significant electrocardiogram | 0 | 0 |
| Electrocardiogram QT prolonged | 0 | 0 |
| Paresthesia | 0 | 0 |
| Seizures | NR | NR |

LEMS = Lambert-Eaton myasthenic syndrome; NR = not reported; SAE = serious adverse event.

[a] Frequency greater than 1 patient per arm.

Source: Clinical Study Report for JPC 3,4-DAPPER.[13]

## Critical Appraisal

### *Internal Validity*

Several elements of the DAPPER study design, while consistent with typical phase II trials, contributed to issues in internal validity.

DAPPER was a double-blind study that employed various strategies to maintain blinding of the patients, investigator, site personnel, and sponsor personnel. However, because the study was designed to use a withdrawal enrichment strategy, unblinding was possible, given that patients in the placebo arm were expected to experience deterioration prior to amifampridine being reinstated. Unblinding in DAPPER may have biased subjective patient-assessed outcome results (e.g., W-SAS, LEFS) and investigator-assessed outcome results (e.g., LEMS-related ADLs) in favour of amifampridine.

The withdrawal design used in DAPPER required patients in the placebo arm to taper their baseline amifampridine dose over a 72-hour period followed by approximately 16 hours of placebo with no amifampridine prior to reinstating their baseline amifampridine dose. Based on feedback from the clinical experts consulted by CADTH for the review, the duration of the taper period and the period of time with only placebo were determined to be sufficient to assess the deterioration of patients (i.e., the efficacy of amifampridine). The duration and design of DAPPER were not appropriate for the assessment of harms because patients enrolled in DAPPER were known to be responsive to amifampridine and on a stable and optimized dosage; therefore, these patients would be familiar with the harms associated with amifampridine and would have already considered the tolerability profile acceptable.

The baseline characteristics were generally balanced between the randomized treatment arms in DAPPER, indicating adequate randomization. More patients in the taper-to-placebo arm (94.4%) were positive for P/Q voltage-gated antibodies compared to patients in the continuous-amifampridine (85.7%) arm. This imbalance is not expected to affect the treatment effect in DAPPER. While none of the patients discontinued the trial, more patients in the taper-to-placebo arm (44.4%) compared to patients treated with continuous

amifampridine (14.3%) had early entry to stage 3 of the trial, where baseline amifampridine was reinstated.

Subgroup analyses based on type of LEMS (paraneoplastic versus primary autoimmune) and age (pediatric versus adult patients) were not performed in DAPPER. Whether or not the treatment effect differs between the subgroups identified as relevant in the CADTH review protocol remains unknown.

The use of the 3TUG as the primary efficacy end point in DAPPER was appropriate, given that it is considered by the clinicians consulted by CADTH to be a clinically relevant tool and an appropriate assessment of function in patients with LEMS. According to the clinical experts, the 3TUG test is considered an appropriate component of assessing treatment response in patients with LEMS in clinic. QMG score (used in the DUKE study; see *Other Relevant Evidence*) is not considered an appropriate or relevant assessment tool for LEMS by the clinical experts consulted by CADTH. The 3TUG and W-SAS outcomes were generally analyzed using appropriate statistical methods. The 30% cut point used for the 3TUG test was considered clinically relevant based on the literature[11] and clinical expert input. Hierarchical testing was not used in DAPPER to account for multiplicity; therefore, firm conclusions cannot be drawn for the secondary outcome (W-SAS).

In the assessment of 3TUG and W-SAS, the last observation during stage 2 was used to inform the end point. Missing data were not accounted for statistically in DAPPER; however, the impact of missing data is expected to be minimal, given that the quantity of missing data was minimal. Outcomes for CMAP, LEFS, and LEMS-related ADLs were reported descriptively, without performing formal statistical testing; while this is consistent with typical phase II trials, it prevents any conclusions being drawn based on these results. Hence, these results can only be considered in terms of how they support the primary results.

### *External Validity*

The withdrawal enrichment strategy used in DAPPER resulted in a highly selected study population of patients who were treatment-experienced and responsive to amifampridine at baseline. Aspects of the trial design created a study population that exhibited a magnitude of treatment response that may not be representative of the Canadian amifampridine-experienced population or generalizable to patients who are amifampridine-naive, including those who are newly diagnosed with LEMS. Several components of the patient eligibility criteria were key in contributing to the enriched study design of DAPPER.

Patients were required to display a sufficiently large response to amifampridine during the baseline observation period. In DAPPER, this definition evolved over the course of the study because it related to several patients (n = 18) failing screening. Throughout the study, the sponsor modified the definition, given that it was determined that patients who were responsive to amifampridine were being unnecessarily excluded from study participation.[13] Ultimately, this criterion was defined as an improvement of greater than or equal to 27% in 3TUG time compared to the 3TUG time before the first morning dose on 2 consecutive days, or an improvement of greater than or equal to 30% after the first morning, afternoon, or evening dose on day 1 plus an improvement of greater than or equal to 12% after the first dose of the morning on day 2. These exclusion criteria would result in a patient population that may be more responsive to study treatment than the Canadian patient population. Thus, the treatment effects estimated by the DAPPER study are likely an

overestimate of the effect on the Canadian patient population that would be eligible to receive amifampridine.

Patients were required to be on a stable regimen of amifampridine for at least 3 months. The criteria related to improvement in LEMS-induced dysfunction within 15 minutes to 30 minutes after the first dose of amifampridine in the morning prevented patients from entering whose LEMS symptoms may have improved or remitted over time. Patients were excluded if they had clinically significant or poorly controlled conditions that, in the opinion of the study personnel, might have posed an unacceptable risk to them if they entered into the study.

Patients in DAPPER were required to be ambulatory while on their usual dose of amifampridine and could not have respiratory failure requiring intubation with no precipitating event or medication while on amifampridine. According to the clinical experts consulted by CADTH, in clinical practice, patients would not be prevented from being treated with amifampridine based on either of these criteria.

Amifampridine is indicated for patients with LEMS who are 6 years of age and older. DAPPER enrolled patients 18 years of age and older, with study patients ranging in age from 23 years to 83 years. Given the general mechanism of action, amifampridine is not expected to have differential impacts on efficacy across age groups, according to the clinical experts consulted for this review.

Overall, the baseline characteristics of patients in DAPPER were generally consistent with the Canadian clinical population currently being treated with amifampridine. However, in DAPPER, only 1 patient had paraneoplastic syndrome. This is inconsistent with the clinical population, in which it is estimated that 50% to 60% of patients have paraneoplastic syndrome. Patients with paraneoplastic LEMS are known to have poorer prognoses; thus, the results of DAPPER may not be representative of these patients.

The use of amifampridine and other LEMS medications at baseline and throughout the study were generally consistent with the treatment regimen of stabilized patients in the Canadian clinical setting. In DAPPER, almost all patients (78.6% in the continuous-amifampridine arm and 83.3% in the taper-to-placebo arm) were taking pyridostigmine as part of their baseline treatment regimen. This was considered higher than what would be seen in the Canadian clinical setting because pyridostigmine is most often used in Canada as a bridging drug for patients diagnosed with LEMS who may be waiting for access to amifampridine; it is often discontinued due to insufficient effectiveness once patients have access to amifampridine. The greater use observed in DAPPER is not expected to affect the results of the trial or their generalizability to Canadians. The primary efficacy end point assessing the 3TUG is consistent with Canadian clinical practice.

## Other Relevant Evidence

This section includes additional relevant studies that were considered to address important gaps in the evidence included in the systematic review.

### DUKE Study

In addition to DAPPER, the sponsor submitted 1 additional study to be reviewed by CADTH. The DUKE study was a prospective, randomized, placebo-controlled, phase II study to evaluate the effectiveness and determine the acute and long-term side effects of

amifampridine in adult patients with LEMS. The DUKE study was a reanalysis of a previously published study by Sanders (2000).[23] Details of the trial characteristics are provided in Table 20.

## Table 20: Details of the DUKE Study

| | | DUKE |
|---|---|---|
| Designs and populations | **Study design** | Prospective, placebo-controlled, randomized, phase II |
| | **Locations** | US |
| | **Randomized (N)** | 26 |
| | **Inclusion criteria** | • Aged > 18 years<br>• Electrophysiologic findings confirming the diagnosis of LEMS<br>• Completion of underlying cancer<br>• Ability and willingness to cooperate with the testing procedures<br>• Muscle weakness on examination<br>• QMG score of 5 or more |
| | **Exclusion criteria[a]** | • History of cardiac arrhythmia or evidence of same on EKG, seizures, or<br>• Epileptiform activity on EEG<br>• Known hepatic, renal, or hematologic disease<br>• Evidence of same on screening blood tests |
| Drugs | **Intervention** | • Amifampridine, 10 mg to 20 mg administered orally 3 or 4 times daily for 6 days to 9 days |
| | **Comparator(s)** | Placebo 3 or 4 times daily, orally |
| Duration | **Phase** | |
| | Blinded | 9 days |
| | Open label | NR |
| Outcomes | **Primary end point** | • QMG score |
| | **Secondary and exploratory end points** | • CMAP<br>• Change in swallowing times<br>• Change in walking times |
| Notes | **Publications** | NA |

CMAP = compound muscle action potential; EEG = electroencephalography; EKG = electrocardiogram; LEMS = Lambert-Eaton myasthenic syndrome; NA = not available; NR = not reported; QMG = quantitative myasthenia gravis.

[a] Inclusion and exclusion criteria were reported as in Sanders (2000).[23]

Source: Clinical Study Report for JPC 3,4 DAP DUKE RCT Supplement.[24]

*Methods*

Eligible patients (N = 26) were randomized in equal numbers, as assigned by a random allocation table, to receive amifampridine
10 mg to 20 mg capsules or placebo 3 or 4 times per day for 6 days to 9 days. According to the Sanders (2000) study design, patients were administered 1 capsule of the study drug 3 times a day for 6 days.[23] Following the sixth day, no study drug was administered for 24 hours to any of the patients. After this, 10 mg or 20 mg amifampridine was again administered 3 times daily, and patients were observed in the hospital for 24 hours.[23] After

the blinded study, patients were given open-label amifampridine and monitored for side effects as long as their symptoms improved.[23]

The primary efficacy measure was the QMG score, which was performed on the last 2 days of treatment with the study drug. Additional efficacy measurements were:

- change in summated CMAP amplitude in 3 muscles (2 in muscles the hand and 1 in the foot)
- change in swallowing times
- change in walking times (this end point was not similar to the 3TUG measure as presented in the pivotal trial).

*Populations*

**Inclusion and Exclusion Criteria**

The inclusion and exclusion criteria were not clearly specified in the study report submitted by the sponsor. Based on the study published by Sanders (2000), patients were eligible for enrolment if the following inclusion criteria were met:[23] more than 18 years of age; electrophysiologic findings confirming the diagnosis of LEMS; completion of appropriate treatment for underlying cancer; ability and willingness to cooperate with the testing procedures; muscle weakness on examination; and a QMG score of 5 or more. The exclusion criteria included a history of cardiac arrhythmia or evidence of same on electrocardiogram; seizures or epileptiform activity on electroencephalography; or known hepatic, renal, or hematologic disease (or evidence of same) on screening blood tests. Women of child-bearing potential were tested for pregnancy and agreed to practice adequate contraception as long as they were receiving amifampridine.

**Baseline Characteristics**

A total of 26 patients were enrolled in the DUKE study. In the ITT population, 57.6% of the study patients were female and 42.3% were male. The proportion of males and females was roughly similar between the amifampridine-treated and placebo-treated groups. The median age of onset, 56.5 years, was similar in both groups. The proportion of patients with SCLC was similar in both groups. The median CMAP values of 1.5 were similar in both groups. The median QMG score at baseline was imbalanced between treatment groups; the median score in the amifampridine group was 8.5, whereas it was 12.3 in the placebo group. The reanalysis submitted by the sponsor noted that 1 of the 5 patients in the placebo group originally reported to have SCLC had non–SCLC. The baseline characteristics of the patients are summarized in Table 21.

## Table 21: Summary of Baseline Characteristics in DUKE (ITT Population)

| Characteristics | DUKE | |
|---|---|---|
| | Amifampridine (N = 12) | Placebo (N = 14) |
| **Gender, n (%)** | | |
| Male | 5 (41.7) | 6(42.9) |
| Female | 7 (58.3) | 8 (57.1) |
| **Age at onset (years)** | | |
| Mean (SD) | 54.3 (14.93) | 56.5 (13.47) |
| Median (range) | 56.5 (31 to 71) | 56.5 (27 to 76) |
| **Patients with SCLC, n (%)** | 4 (33.3) | 5 (35.7) |
| **Baseline QMG** | | |
| Mean (SD) | 11.8 (6.38) | 11.7 (3.86) |
| Median (range) | 8.5 (5.5 to 25.5) | 12.3 (5.0 to 19.5) |
| **Baseline CMAP** | | |
| Mean (SD) | 1.7 (1.30) | 1.7 (0.97) |
| Median (range) | 1.5 (0.2 to 4.1) | 1.5 (0.6 to 3.8) |

CMAP = compound muscle action potential; ITT = intention to treat; QMG = quantitative myasthenia gravis score; SCLC = small cell lung cancer; SD = standard deviation.
Source: JPC 3,4-DAP DUKE RCT Supplement.[24]

*Interventions*

Eligible patients were randomized to receive amifampridine 10 mg to 20 mg 3 or 4 times per day or placebo 3 or 4 times per day.[24]

*Outcomes*

The primary efficacy measure was the change from baseline in QMG score. Changes in the amplitude of CMAPs elicited by nerve stimulation were used as a secondary measure. Other outcomes evaluated in the sponsor's reanalysis were change in swallowing times and change in walking times. The changes in swallowing and walking times were not reported in the Sanders (2000). study.[23]

**Quantitative Myasthenia Gravis Score**

In each patient, the average of QMG scores obtained on the first 2 days of hospitalization were to be compared with the average of scores obtained on the fourth and fifth days of blinded drug administration. The populations for analysis were the PP and ITT populations. Final QMG scores were measured from day 5 to day 8, with 1 patient being measured on day 9. The sponsor conducted 2 sensitivity analyses of the ITT population: 1 analysis including only a single post-baseline QMG score, and 1 analysis using only the last available post-baseline QMG score for all patients.

**Compound Muscle Action Potential**

Three CMAPs were measured from each 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 summated CMAP was the sum of the mean CMAP values from the 3 muscles. The peak negative CMAP amplitude was measured in the abductor digiti minimi and abductor pollicis brevis muscles of 1 hand and the extensor digitorum brevis muscle in 1 foot.[23] The

average of the summated CMAPs obtained on 2 consecutive days before beginning the study drug was used as the baseline CMAP amplitude, and the average of the summated CMAPs obtained on the fourth and fifth days of study drug administration was used as the post-baseline CMAP amplitude.

The sponsor conducted 2 sensitivity analyses of the ITT population: 1 analysis including only a single post-baseline CMAP, and 1 analysis using only the last available post-baseline CMAP for all patients.

**Change in Swallowing Times**

The additional efficacy measure submitted, which was not part of the original study, was the improvement in swallowing time; this was measured in the ITT population. Change in swallowing times measures the percentage change from baseline in the time needed to swallow 150 mL of water.[24]

To account for the effect of missing data, the sponsor conducted a sensitivity analysis of the ITT population using only the last available post-baseline measure for all patients.

**Change in Walking Times**

The additional efficacy measure submitted, which was not part of the previous publication, was improvement in walking time; this was measured in the ITT population. Change in walking times measures the percentage change from baseline in the time needed to walk 150 feet with 1 turn.[24]

To account for the effect of missing data, the sponsor conducted a sensitivity analysis of the ITT population using only the last available post-baseline measure for all patients.

*Statistical Analysis*

Once the 26 patients had completed the blinded trial, the assignment code was broken, and the difference in average QMG scores obtained before and during blinded drug administration was compared in the amifampridine and placebo groups using a 1-sided, 2-sample t-test. As per Sanders (2000),[23] the data were skewed and the descriptive statistics were summarized for continuous variables as medians and interquartile ranges using the Wilcoxon rank sum test to evaluate group differences instead of a t-test, which had been the original study plan. Fisher's exact test was used to evaluate group differences in categorical variables. Based on the results of a preliminary study, it was estimated that 13 patients were required for an 80% probability of demonstrating statistical significance at the 0.05 level.

Descriptive statistics for continuous variables were summarized as medians and interquartile ranges using the 2-sided, 2-sample Wilcoxon rank sum test to evaluate group differences. Fisher's exact test was used to evaluate group differences in categorical variables.

**Quantitative Myasthenia Gravis Score**

The populations for analyses were the PP and ITT populations. The sponsor conducted 2 sensitivity analyses of the ITT population: 1 analysis including only a single post-baseline QMG score, and 1 analysis using only the last available post-baseline QMG score for all patients.

**Compound Muscle Action Potential**

The sponsor conducted 2 sensitivity analyses of the ITT population: 1 analysis including only a single post-baseline CMAP, and 1 analysis using only the last available post-baseline CMAP for all patients.

**Change in Swallowing Times**

Change in swallowing times was measured in the ITT population. To account for the effect of missing data, the sponsor conducted a sensitivity analysis of the ITT population using only the last available post-baseline measure for all patients.

**Change in Walking Times**

Change in walking times was measured in the ITT population. To account for the effect of missing data, the sponsor conducted a sensitivity analysis of the ITT population using only the last available post-baseline measure for all patients.

**Analysis Populations**

The sponsor performed a reanalysis of the efficacy measurements in 2 analysis populations:

- *ITT population*: all randomized patients who received at least 1 dose of amifampridine or placebo during the double-blind phase
- *PP population*: all randomized patients who received at least 1 dose of amifampridine 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).

### *Patient Disposition*

The reanalysis submitted by the sponsor did not present the patient disposition. Therefore, the patient disposition is reported from Sanders (2000).[23] Thirty-seven patients were found to be eligible for the trial. Eleven patients were not randomized; 26 patients were randomized; 14 patients received placebo; and 12 patients received amifampridine. In the placebo group, 14 patients completed the trial. Similarly, 12 patients completed the trial in the amifampridine group.

### *Exposure to Study Treatments*

Patients in the study took 1 capsule of the study drug 3 or 4 times per day for 6 days to 9 days. Patients in the placebo arm took identical capsules containing lactose alone.[23] Sanders (2000)[23] reported that after completing the blinded phase, 25 patients took open-label amifampridine.

### *Efficacy*

**Quantitative Myasthenia Gravis Score**

The mean (SD) change from baseline in QMG score was –2.0 (2.16) in the amifampridine group and 0.2 (1.65) in the placebo group in favour of amifampridine (P = 0.015). The results of the sensitivity analysis aligned with the primary efficacy analysis.

## Table 22: Quantitative Myasthenia Gravis Score Results (Per-Protocol Population)

| Characteristics | DUKE | |
|---|---|---|
| | Amifampridine (N = 12) | Placebo (N = 13) |
| **Baseline** | | |
| Mean (SD) | 11.8 (6.38) | 11.1 (3.26) |
| Median (range) | 8.5 (5.5 to 25.5) | 11.5 (5.0 to 15.5) |
| **Post-baseline** | | |
| Mean (SD) | 9.8 (6.90) | 11.3 (3.19) |
| Median (range) | 6.5 (3.0 to 25.0) | 12.5 (5.0 to 14.5) |
| P value[a] | 0.220 | |
| **Change from baseline** | | |
| Mean (SD) | –2.0 (2.16) | 0.2 (1.65) |
| Median (range) | –2.0 (–6.5 to 0.5) | –0.5 (–1.5 to 4.0) |
| P value[a] | 0.015 | |

SD = standard deviation.

[a] P value is derived from a 2-sided, 2-sample Wilcoxon rank sum test, normal approximation.

Source: JPC 3,4-DAP DUKE RCT Supplement.[24]

**Compound Muscle Action Potential**

The mean (SD) change from baseline in the CMAP measure was 1.5 (1.54) in the amifampridine group and –0.0 (0.54) in the placebo group (P = 0.011). The mean (SD) percentage change from baseline was 163.1 (221.7) in the amifampridine group and 3.0 (30.15) in the placebo group (P = 0.017).

## Table 23: CMAP Results (ITT Population From Sensitivity Analysis Using Last Available Post-Baseline CMAP Measures for All Patients)

| Characteristics | DUKE | |
|---|---|---|
| | Amifampridine (N = 12) | Placebo (N = 14) |
| **Baseline** | | |
| Mean (SD) | 1.7 (1.30) | 1.7 (0.97) |
| Median (range) | 1.5 (0.2 to 4.1) | 1.5 (0.6 to 3.8) |
| **Post-baseline** | | |
| Mean (SD) | 3.2 (2.13) | 1.7 (0.97) |
| Median (range) | 3.5 (0.3 to 6.3) | 1.4 (0.5 to 3.9) |
| P value[a] | 0.105 | |
| **Change from baseline** | | |
| Mean (SD) | 1.5 (1.54) | –0.0 (0.54) |
| Median (range) | 1.2 (–0.3 to 4.5) | –0.1 (–1.4 to 1) |
| P value[a] | 0.011 | |
| **Percentage change from baseline** | | |
| Mean (SD) | 163.1 (221.7) | 3.0 (30.15) |
| Median (range) | 52.3 (–35.2 to 566.7) | –6.3(–6.8 to 81.3) |

| Characteristics | DUKE | |
|---|---|---|
| | Amifampridine (N = 12) | Placebo (N = 14) |
| P value[a] | 0.017 | |

CMAP = compound muscle action potential; ITT = intention to treat; SD = standard deviation.

[a] P value is derived from a 2-sided, 2-sample Wilcoxon rank sum test, normal approximation.

Source: JPC 3,4-DAP DUKE RCT Supplement.[24]

### Change in Swallowing Time

The mean (SD) change from baseline in swallowing time was –3.8 (3.29) in the amifampridine group and 1.5 (12.15) in the placebo group (P = 0.112). The mean (SD) percentage change from baseline was –28.1 (19.97) in the amifampridine group and –1.2 (57.91) in the placebo group (P = 0.239).

## Table 24: Change in Swallowing Time After Therapy (ITT Population From Sensitivity Analysis Using Last Available Post-Baseline Measures for All Patients)

| Characteristics | DUKE | |
|---|---|---|
| | Amifampridine (N = 11) | Placebo (N = 14) |
| **Baseline (sec)** | | |
| Mean (SD) | 13.0 (7.93) | 14.1 (13.15) |
| Median (range) | 11 (4.0 to 30.5) | 10.5 (0.0 to 45.0) |
| **Post-baseline (sec)** | | |
| Mean (SD) | 9.3 (7.07) | 15.5 (19.37) |
| Median (range) | 8.0 (3.0 to 27.0) | 8.5 (0.0 to 72.0) |
| P value[a] | 0.763 | |
| **Change from baseline (sec)** | | |
| Mean (SD) | –3.8 (3.29) | 1.5 (12.15) |
| Median (range) | –2.7 (–9.3 to 0.0) | –0.0 (–15.0 to 35.0) |
| P value[a] | 0.112 | |
| **Percentage change from baseline (sec)** | | |
| Mean (SD) | –28.1 (19.97) | –1.2 (57.91) |
| Median (range) | –25.0 (–60.8 to 0.0) | –14.6 (–99.4 to 108.0) |
| P value[a] | 0.239 | |

ITT = intention to treat; SD = standard deviation; sec = seconds.

[a] P value is derived from a 2-sided, 2-sample Wilcoxon rank sum test, normal approximation.

Source: JPC 3,4-DAP DUKE RCT Supplement.[24]

### Change in Walking Time

The mean (SD) change from baseline in walking time was –16.2 (12.40) in the amifampridine group and –15.6 (25.12) in the placebo group (P = 0.648). The mean (SD) percentage change from baseline was –24.3 (–52.4 to –15.3) in the amifampridine group and –15.2 (–40.8 to 27.8) in the placebo group (P = 0.239).

## Table 25: Change in Walking Time After Therapy (ITT Population From Sensitivity Analysis Using Last Available Post-Baseline Measures for All Patients)

| Characteristics | DUKE | |
|---|---|---|
| | Amifampridine (N = 9) | Placebo (N = 11) |
| **Baseline (sec)** | | |
| Mean (SD) | 49.2 (16.12) | 79.1 (39.10) |
| Median (range) | 42.5 (34.5 to 82.0) | 70.5 (29.5 to 147.0) |
| **Post-baseline (sec)** | | |
| Mean (SD) | 33.0 (6.20) | 63.4 (32.41) |
| Median (range) | 33 (22.0 to 42.0) | 53 (23.0 to 120.0) |
| P value | 0.012 | |
| **Change from baseline (sec)** | | |
| Mean (SD) | –16.2 (12.40) | –15.6 (25.12) |
| Median (range) | –13.5 (–43.0 to –5.5) | –9.5 (–60.0 to 25.0) |
| P value | 0.648 | |
| **Percentage change from baseline (sec)** | | |
| Mean (SD) | –30.0 (13.23) | –16.9 (24.62) |
| Median (range) | –24.3 (–52.4 to –15.3) | –15.2 (–40.8 to 27.8 |
| P value | 0.224 | |

ITT = intention to treat; SD = standard deviation; sec = seconds.

[a] P value is derived from a 2-sided, 2-sample Wilcoxon rank sum test, normal approximation.

Source: JPC 3,4-DAP DUKE RCT Supplement.[24]

*Harms*

AEs and SAEs were not presented in the study supplement submitted by the sponsor for this review. The AEs reported in the publication[23] were perioral tingling and digital paresthesia in 4 of 14 patients while they were taking blinded amifampridine and in 8 of 22 patients while they were taking open-label amifampridine.

The sponsor conducted a retrospective review of the available safety information and identified 3 patients who reported SAEs: 1 patient who had recently been treated for SCLC and randomized to placebo experienced anxiety, respiratory difficulties, difficulty speaking, and chest discomfort; 1 patient randomized to amifampridine was hospitalized for muscle weakness about 1 week after completing the study; and 1 patient randomized to placebo died of pulmonary complications of lung cancer approximately 1 month after starting open-label treatment with amifampridine.

Change in echocardiogram was identified as a notable harm in the CADTH review protocol. The sponsor presented the safety results of the QT interval (corrected for heart rate) obtained from electrocardiograms during the study. The mean (SD) change from baseline for the echocardiogram in the amifampridine group was 0.5 (13.46) and –4.4 (14.64) in the placebo group.

## Table 26: Effect of Amifampridine on the QTc Interval (ITT Population)

| Characteristics | DUKE | |
|---|---|---|
| | Amifampridine (N = 12) | Placebo (N = 13) |
| **Baseline** | | |
| Mean (SD) | 417.4 (20.80) | 412.5 (20.44) |
| Median (range) | 418.5 (387 to 448) | 401.0 (380 to 449) |
| **Post-baseline** | | |
| Mean (SD) | 417.9 (22.99) | 408.1 (18.42) |
| Median (range) | 414.0 (381 to 470) | 403.0 (384 to 447) |
| **Change from baseline (post-baseline minus baseline)** | | |
| Mean (SD) | 0.5 (13.46) | –4.4 (14.64) |
| Median (range) | –0.5 (–24 to 22) | –2.0 (–27 to 29) |

ITT = intention to treat; QTc = QT interval corrected for heart rate; SD = standard deviation.

Source: JPC 3,4-DAP DUKE RCT Supplement.[24]

*Critical Appraisal*

**Internal Validity**

The DUKE study was a reanalysis of a previously published study. Details of the statistical analysis plan for these reanalyses were not included in the study report provided by the sponsor, and there was not enough information for CADTH to conduct a detailed critical appraisal of the statistical methodology. Given this, it remains uncertain whether the original randomization was maintained between groups. However, baseline characteristics provided for the reanalysis were generally well-balanced between treatment groups (with the exception of median QMG score), so this is unlikely to have an impact on the study results. Details regarding the sample size calculation were not provided.

The blinding process was not described in detail; therefore, CADTH cannot comment on whether patients and investigators were adequately blinded to the study treatments received.

The study design included patients who were previously receiving LEMS-related treatment, but no details were provided regarding prior treatment experience or the washout period. Therefore, it is not known whether the carryover effects of previous treatments may have affected the results of the DUKE study.

**External Validity**

Given that this was a single-centre study and that details about patients were limited, it is unclear whether the results are generalizable to patients with LEMS in Canada. The study does not provide details about patients' previous treatment exposures or experiences with amifampridine. The primary efficacy outcome was QMG score; however, the clinical experts consulted by CADTH agreed that QMG score is not considered an appropriate or relevant assessment tool for LEMS.

### Oh (2009) and McEvoy (1989)

Two additional studies, Oh (2009)[14] and McEvoy (1989),[25] were identified in the literature review by CADTH. Oh (2009) was a randomized, double-blind crossover study that

investigated the clinical and electrophysiological efficacy of amifampridine in patients with LEMS. McEvoy (1989) was an open-label, prospective, double-blind, placebo-controlled crossover study of 12 patients with LEMS to determine the efficacy and safety of amifampridine. Details of the trial characteristics are provided in Table 27.

## Table 27: Details of Oh (2009) and McEvoy (1989)

| | | Oh (2009) | McEvoy (1989) |
|---|---|---|---|
| Designs and populations | **Study design** | Randomized, double-blind crossover | Open-label period followed by double-blind, placebo-controlled crossover period |
| | **Locations** | US | US |
| | **Randomized (N)** | 7 | 12 |
| | **Inclusion criteria** | Electrophysiologically confirmed LEMS | • Electrophysiologically confirmed LEMS, which included:<br>○ a decrement of more than 10% during repetitive stimulation with 2 Hz<br>○ a facilitation of more than 200% after 10 seconds of exercise in 2 different nerve-muscle combinations<br>• Stable or progressive weakness sufficient to give a strength subscore of 20 on the neurologic disability score |
| | **Exclusion criteria** | NR | NR |
| Drugs | **Intervention** | • A maximum of 75 mg/day over 3 days in a 3-day trial<br>• A maximum of 80 mg over 8 days in an 8-day trial | • Increasing dosages of amifampridine, up to 25 mg 4 times a day |
| | **Comparator(s)** | Placebo | Placebo |
| Duration | **Phase** | | |
| | Run-in | | 8 days prior to randomization |
| | Double-blind | 8-day trial in 3 cases<br>3-day trial in 4 cases | First 3 days to receive placebo or study drug<br>Second 3 days to receive alternative capsules |
| | Follow-up | 12 years | 3 months |
| Outcomes | **Outcomes** | • Neurological status: subjective symptoms; LEMS classification; Medical Research Council score; quantitative myasthenia gravis score<br>• Electrophysiological outcome: repetitive nerve stimulation in abductor digiti quinti muscle | • Objective measures<br>○ neurological disability scores<br>○ isometric strength<br>○ upper-extremity strength<br>• Electrophysiological improvement |
| Notes | **Publications** | Oh (2009)[14] | McEvoy (1989)[25] |

Hz = hertz; LEMS = Lambert-Eaton myasthenic syndrome; NR = not reported.

Source: Oh (2009)[14], McEvoy (1989).[25]

*Methods*

In Oh (2009), the assignment of amifampridine or placebo was based on a random number table, and patients and physicians were blinded. Initially, the durations of both the amifampridine and placebo phases were 8 days. However, these were amended to 3 days each to shorten the study duration. There was no ‘‘drug washout period’’ between the amifampridine and placebo groups because amifampridine has a short duration of action, lasting around 3 hours.[14]

In McEvoy (1989),[25] amifampridine was administered orally in an open-label fashion for the first 8 days of treatment. Studies were repeated during this time to assess efficacy and safety. Following the open-label phase, patients entered the double-blind crossover phase. During the first 3 days of this phase, patients were randomized to receive the study drug. Through the next 3 days, alternative capsules were given. The trial duration was 15 days.

*Populations*

**Inclusion and Exclusion Criteria**

Patients in both studies had to have a confirmed diagnosis of LEMS. In the Oh (2009) study, patients were diagnosed with LEMS using the combined findings of fluctuating muscle weakness, diminished or absent reflexes, and an increment of more than 60% in CMAP after brief exercise (post-exercise facilitation), or 50 hertz for 1 second on a repetitive nerve stimulation. There were no clear exclusion criteria presented in the study.

In the McEvoy (1989) study, the electrophysiological criterion used to diagnose LEMS was a decrement of 10% during repetitive stimulation with 2 hertz and a post-exercise facilitation of more than 200% after 10 seconds of exercise in 2 different nerve-muscle combinations. Although no clear exclusion criteria were listed, 1 patient who was receiving immunosuppressive therapy was excluded from the study because they no longer exhibited LEMS symptoms.

**Baseline Characteristics**

The Oh (2009) study recruited 8 patients with LEMS (7 males [87.5%] and 1 female [12.5%]) over a 12-year period from 1996 to 2008. All patients had fluctuating leg weakness, proximal leg weakness, and diminished or absent reflexes at the time of diagnosis. Three patients (37.5%) had SCLC. The electrophysiological diagnostic criteria were fulfilled by all patients; i.e., at the time of diagnosis, patients had: low CMAP amplitude (less than or equal to 4.7 millivolts [mV]); a decremental response at low-rate stimulation (greater than or equal to 10.5%); post-tetanic facilitation (post-exercise facilitation greater than or equal to 110%) in the abductor digiti quinti muscle in 7 patients, and anterior tibialis muscle in 1 patient. Voltage-gated calcium channel antibodies were positive in 4 out of 6 tested patients.[14] Seven symptomatic patients had had a stable course in the preceding 3 months. Two patients were not on any medication. Two patients were using prednisone, 4 were on pyridostigmine, and 2 were on guanidine hydrochloride.[14]

The McEvoy (1989) study recruited 12 patients. Eight (66.6%) were female and 4 (33.3%) were male. Their ages ranged from 34 years to 75 years (mean = 65). Seven (58.33%) patients had cancer: 1 had renal-cell carcinoma, 1 had endometrial cancer, 2 had small cell carcinoma of the lung, 1 had cervical cancer, 1 had basal cell carcinoma, and 1 had breast carcinoma. Five patients had autoimmune disorders, including Hashimoto’s thyroiditis,

rheumatoid arthritis, vitiligo, pernicious anemia, psoriasis, and type I diabetes mellitus. Three patients had more than 1 such disorder.[25]

### *Interventions*

In the Oh (2009) study, amifampridine was provided in 10 mg tablets, while the placebo, which looked like the amifampridine tablets, contained lactose. Three 10 mg tablets (30 mg total daily dose) of amifampridine or placebo were given on the first day of treatment. The dose was increased to a maximum of 75 mg/day over 3 days in the 3-day trial and to a maximum of 80 mg over 8 days in the 8-day trial. During the baseline evaluation, pyridostigmine and guanidine hydrochloride were discontinued for 24 hours and 3 days, respectively. Patients who were taking an immunotherapeutic drug could continue the treatment during the trial.

In the McEvoy (1989) study, patients were randomly assigned to receive amifampridine or placebo orally; the dosage was determined based on the maximum tolerable dose identified during the open-label phase of the trial. Ten patients who were being treated with acetylcholinesterase inhibitors had to discontinue treatment 4 days prior to study entry. Other prior treatments included prednisone, guanidine, plasmapheresis, and azathioprine. No washout period was described.

### *Outcomes*

Neither the Oh nor the McEvoy study included a clear description of primary and secondary outcomes. The main outcomes assessed in the Oh study[14] were:

- a subjective symptom score (a general descriptive term [severe = 3; moderate = 2; mild = 1; none = 0] was assigned for general fatigability, walking difficulty, and dryness of the mouth)
- LEMS classification (based on the MRC grade of the pelvic girdle [iliopsoas] muscles, severity of disease was assessed as follows: 0 [asymptomatic] = 5; I [mild] = 4; II [moderate] = 3; and III [severe] = 0 to 2)
- MRC score (muscle strength was examined in 22 muscles, including 2 neck muscles, 10 arm muscles, and 10 leg muscles; a score of 0.33 was added to the [+] grade and a score of 0.33 was subtracted from the [–] grade; note that normal individuals have an MRC score of 110)
- QMG score
- CMAP.

The main outcomes in the McEvoy 1989 study were:

- neurological disability scores (the score sheet indexes are scored; a score of 0 denotes no deficit, 1 = mild weakness, 2 = moderate weakness, 3 = severe weakness, and 4 = no movement)
- isometric strength
- electrophysiological improvement.

### *Statistical Analysis*

Oh (2009) measured the difference between placebo and baseline values, and this placebo change was compared to the difference between amifampridine and baseline or placebo values. An unpaired t-test and Pearson chi-square test were used for the statistical analysis. $P < 0.05$ was considered statistically significant.

McEvoy (1989) quantitatively measured severity before therapy and during maximal doses of amifampridine using paired t-tests. Values were reported as mean ± SE.

### *Patient Disposition*

One patient in the Oh study withdrew from the second phase because of a drug side effect in the first phase.[14] Four patients continued amifampridine in an open-label design following the randomized phase of the trial.

In the McEvoy study, 12 patients were recruited, and 3-month follow-up data were available for all of them. Further patient disposition has not been reported.

### *Exposure to Study Treatments*

The average daily dose of the drug received during the study was not reported in the Oh study. One patient was given up to 70 mg per day for 3 months.[14]

In the McEvoy study, 10 patients tolerated the full dosage of 25 mg of amifampridine 4 times a day during the open-label phase and received this dosage during the crossover phase. The average maintenance dosage was 20 mg 4 times a day.[25] After 3 months, 4 patients had pyridostigmine added to their regimens.

### *Efficacy*

Oh reported that the mean ± SE for the subjective symptoms score change was –0.69 ± 0.86 in the amifampridine group and 0.50 ± 0.84 in the placebo group (P = 0.0112).[14] The mean ± SE for the LEMS class change was –0.85 ± 0.69 in the amifampridine group and 0.33 ± 0.52 in the placebo group (P = 0.0017).[14] The mean ± SE for the MRC score change was 1.23 ± 1.00 in the amifampridine group and –0.12 ± 0.50 in the placebo group (P = 0.0062).[14] The mean ± SE for the QMG score change was –2.36 ± 2.25 in the amifampridine group and 0.40 ± 1.14 in the placebo group (P = 0.0223).[14] The mean ± SE for CMAP change was 1.79 ± 2.05 in the amifampridine group and –0.90 ± 1.78 in the placebo group (P = 0.0246).[14]

McEvoy reported that the neurological disability scores during the double-blind phase of treatment were 22 in the amifampridine group and 35 in the placebo group (P < 0.05 in the active drug group).[25] The results are summarized in Figure 5. Isometric strength was measured in the arm and leg.[25] The results for isometric strength are summarized in Figure 6.

## Figure 5: McEvoy (1989): Average Neurological Disability Score

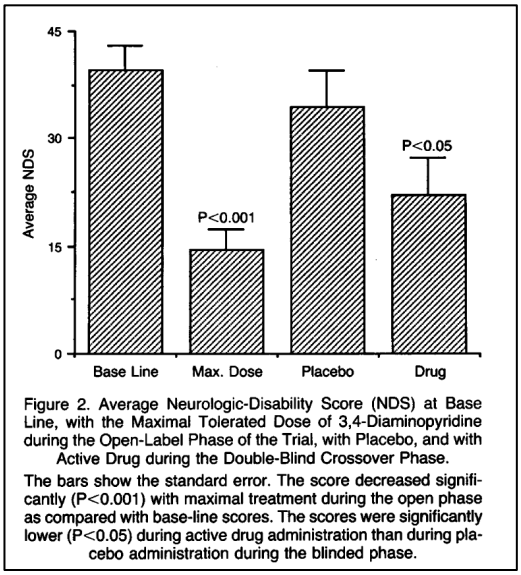



Figure 2. Average Neurologic-Disability Score (NDS) at Base Line, with the Maximal Tolerated Dose of 3,4-Diaminopyridine during the Open-Label Phase of the Trial, with Placebo, and with Active Drug during the Double-Blind Crossover Phase.

The bars show the standard error. The score decreased significantly (P<0.001) with maximal treatment during the open phase as compared with base-line scores. The scores were significantly lower (P<0.05) during active drug administration than during placebo administration during the blinded phase.

Max. = maximal; NDS = neurological disability score.

Source: 3,4-Diaminopyridine in the treatment of Lambert-Eaton Myasthenic Syndrome, Kathleen M. McEvoy, Anthony J. Windebank, Jasper R. Daube, and Phillip A. Low, 3,4-Diaminopyridine in the treatment of Lambert-Eaton Myasthenic Syndrome, Volume 321, Page No 15671-1571. Copyright © (1989) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[25]

## Figure 6: McEvoy (1989): Isometric Strength

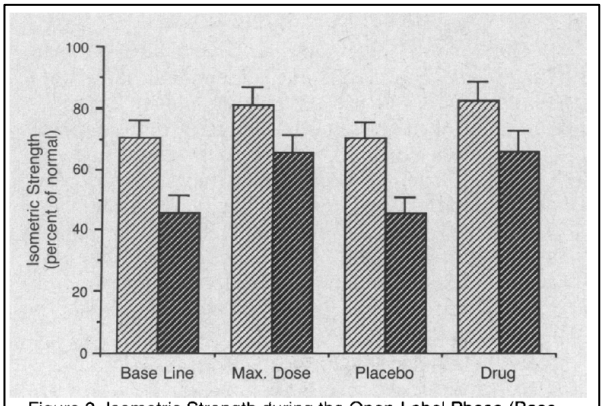



Figure 3. Isometric Strength during the Open-Label Phase (Base Line and Maximal Dose) and during the Double-Blind Crossover Phase of the Trial (Placebo and Active Drug).

The light bars show arm strength as a percentage of normal. The dark bars show leg strength as a percentage of normal. The T-bars show the standard error. Arm strength and leg strength during maximal therapy were significantly higher (P<0.001) than base-line values during the open phase. Arm strength and leg strength during drug therapy were significantly higher (P<0.005 and P<0.001, respectively) than values obtained during placebo administration during the blinded phase.

Max. = maximal.

Source: 3,4-Diaminopyridine in the treatment of Lambert-Eaton Myasthenic Syndrome, Kathleen M. McEvoy, Anthony J. Windebank, Jasper R. Daube, and Phillip A. Low, 3,4-Diaminopyridine in the treatment of Lambert-Eaton Myasthenic Syndrome, Volume 321, Page No 15671-1571. Copyright © (1989) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[25]

In the McEvoy 1989 study, during the double-blind phase, the average resting, facilitated, and decrement CMAPs in the amifampridine group were 5.1 ± 0.9 mV, 9.6 ± 0.8 mV, and 21.6 ± 2.2% in the arm and 3.2 ± 0.7 mV, 4.9 ± 0.9 mV, and 20.4 ± 2.6% in the leg, respectively. The average resting, facilitated, and decrement CMAPs in the placebo group were 2.8 ± 0.6 mV, 7.6 ± 0.7 mV, and 28.6 ± 3.0% in the arm and 1.8 ± 0.4 mV, 3.4 ± 0.7 mV, and 25.8 ± 2.3% in the leg, respectively.[25] The average resting, facilitated, and decrement CMAPs at 3 months (n = 12) were 4.9 ± 1.0 mV, 12.0 ± 0.9 mV, and 21.4 ± 3.2% in the arm and 2.8 ± 0.6 mV, 5.1 ± 0.9 mV, and 19.6 ± 3.2% in the leg, respectively.[25] At 9 months (n = 11), the average resting CMAP was 5.1 ± 1.0 mV in the arm and 3.1 ± 0.7 mV in the leg.[25] At 15 months (n = 9), it was 5.5 ± 1.3 mV and 3.2 ± 0.8 mV in the arm and leg, respectively.[25] The main efficacy measures evaluated in the McEvoy 1989 are summarized in Figure 7.

## Figure 7: Average Compound Muscle Action Potential in McEvoy (1989)

| VARIABLE | COMPOUND-MUSCLE-ACTION POTENTIAL | | | | |
|---|---|---|---|---|---|
| | BASE LINE | MAXIMAL DOSE | PLACEBO | ACTIVE DRUG | 3-MO FOLLOW-UP |
| Arm† | | | | | |
| Resting (mV) | 2.9±0.4 | 5.0±0.5‡ | 2.8±0.6 | 5.1±0.9§ | 4.9±1.0 |
| Facilitated (mV)¶ | 7.7±0.5 | 10.4±0.9 | 7.6±0.7 | 9.6±0.8 | 12.0±0.9 |
| Decrement (%) | 26.7±2.4 | 21.7±1.9 | 28.6±3.0 | 21.6±2.2 | 21.4±3.2 |
| Leg‖ | | | | | |
| Resting (mV) | 1.6±0.4 | 3.1±0.6‡ | 1.8±0.4 | 3.2±0.7** | 2.8±0.6 |
| Facilitated (mV)¶ | 3.2±0.8 | 5.8±1.1 | 3.4±0.7 | 4.9±0.9 | 5.1±0.9 |
| Decrement (%) | 22.9±2.3 | 20.2±2.2 | 25.8±2.3 | 20.4±2.6 | 19.6±3.2 |

*Plus–minus values are means ±SE.

†The following nerve–muscle combinations were measured in the arm: ulnar–hypothenar (n = 7), median–abductor pollicis brevis (n = 3), and musculocutaneous–biceps (n = 2).

‡P<0.001 for the comparison with base-line values during the open phase.

§P<0.005 for the comparison with placebo values during the blinded phase.

¶Facilitated amplitudes were measured 10 seconds after 10 seconds of exercise.

‖The following nerve–muscle combinations were measured in the leg: peroneal–anterior tibialis (n = 11) and tibial–abductor hallucis (n = 1).

**P<0.010 for the comparison with placebo values during the blinded phase.

mo = months; mV = millivolts; SE = standard error.

Source: 3,4-Diaminopyridine in the treatment of Lambert-Eaton Myasthenic Syndrome, Kathleen M. McEvoy, Anthony J. Windebank, Jasper R. Daube, and Phillip A. Low, 3,4-Diaminopyridine in the treatment of Lambert-Eaton Myasthenic Syndrome, Volume 321, Page No 15671-1571. Copyright © (1989) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[25]

### *Harms*

In the Oh (2009) study, paresthesia was reported in 2 patients treated with amifampridine. One experienced a heat sensation in the body and the other experienced numbness of the tongue and lips.

In the McEvoy (1989) study, 10 out of 12 patients had perioral or acral paresthesias after 30 minutes of administering amifampridine. After 10 months of treatment, 1 patient had a seizure after receiving a maximal dose of 100 mg of amifampridine. The electroencephalography showed no changes before or during treatment. After lowering the dose to 40 mg, the patient did not show seizure recurrence.

### Internal Validity

In both studies, owing to insufficient information, we cannot determine whether the sample sizes were adequate, or whether methods for controlling for type I error were applied. Given that the primary and secondary outcomes were not clearly defined, our ability to interpret the results is limited. In the Oh study, the lack of a washout period during the crossover phase in patients with LEMS who were prescribed amifampridine could lead to a treatment bias. The efficacy of clinical and electrophysiological outcomes measured did not demonstrate clinical validation. In the absence of clearly reported baseline characteristics, we cannot estimate whether the treatment groups were balanced. As previously described, the use of the QMG score is questionable as a clinically relevant efficacy outcome for patients with LEMS in Canada.

### External Validity

Both studies had patients with malignancies. However, details about the management of these patients during the trial have not been provided. In both studies, patients were recruited from a single centre in the US; therefore, results may not be generalizable to Canadian patients with LEMS. However, the clinical experts consulted by CADTH mentioned that nearly two-thirds of their patients were prescribed 60 mg of amifampridine, while those with severe LEMS cases could be prescribed up to 100 mg of amifampridine. These prescribed dosages are similar to the dosages used in the 2 trials; however, a conclusion on the similarity of the treatment regimen cannot be made.

In the Oh (2009) study of the 7 patients in the trial, 2 patients were not on any medication at the time of the trial; however, no information regarding earlier experience with amifampridine was provided. It is unclear whether these 2 patients were amifampridine-naive. Due to the sparse information regarding amifampridine exposure in the patient population studied, the results of the treatment effects cannot be generalized to all patients with LEMS. In the McEvoy (1989) study, information regarding previous amifampridine treatment was not reported. As a result, the study is prone to similar external validity issues as the Oh (2009) study.

Both studies provided limited information about patients' previous exposures to other LEMS treatments.

# Discussion

## Summary of Available Evidence

One pivotal trial, DAPPER (N = 32), was included in the CADTH systematic review. DAPPER was a phase II, multi-centre, randomized, double-blind, placebo-controlled withdrawal study that aimed to confirm the safety and evaluate the efficacy of amifampridine for the treatment of weakness associated with LEMS in adult patients with known clinically active LEMS who had continuous, stable use of amifampridine for at least 3 months.

DAPPER consisted of 3 stages. Stage 1 involved 2 days of baseline assessments. Patients who responded sufficiently to amifampridine as indicated by the 3TUG test were eligible for enrolment in DAPPER and entered stage 2, where they were centrally randomized in a 1:1 ratio to continue their current treatment regimen (group A, continuous amifampridine) or to withdraw from amifampridine (group B, taper to placebo) for up to 3 and a half days. Patients in the placebo arm had their baseline amifampridine tapered over a 72-hour period followed by approximately 16 hours of placebo. Baseline amifampridine was restored during stage 3, in which patients were observed for half a day or until clinically stable.

The primary efficacy end point in DAPPER 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 the withdrawal of active medication (stage 2) compared with the time-matched average of the 3TUG assessments during stage 1. DAPPER categorized this as a deterioration of greater than 30% in 3TUG time. The secondary efficacy end point in DAPPER was the W-SAS, which was assessed at the end of stage 2 compared to the baseline. Analyses of other outcomes (e.g., CMAP, LEFS, LEMS-related ADLs) were descriptive. DAPPER’s key limitations related to internal validity issues — such as the increased potential for unblinding and descriptive assessment of outcomes — and generalizability issues. The study design and eligibility criteria led to a study population that consisted of patients who were treatment-experienced and responsive to amifampridine at baseline and whose magnitude of treatment response may not be representative of the Canadian amifampridine-experienced population or generalizable to amifampridine-naive patients, including those newly diagnosed with LEMS.

Other relevant evidence included in this review included the DUKE study and studies by Oh (2009)[14] and McEvoy (1989).[25] The DUKE study was a phase II, prospective, randomized, placebo-controlled study designed to evaluate the effectiveness and determine the acute and long-term side effects of amifampridine in adult patients with LEMS.[24] The Oh[14] and McEvoy[25] studies were identified in the literature review by CADTH. The Oh study was a randomized, double-blind, crossover study that investigated the clinical and electrophysiological efficacy of amifampridine in patients with LEMS.[14] The McEvoy study was an open-label, prospective, double-blind, placebo-controlled crossover study of 12 patients with LEMS that aimed to determine the efficacy and safety of amifampridine.[25]

## Interpretation of Results

### Efficacy

In DAPPER, disability progression was assessed using the 3TUG test after withdrawing the study drug (stage 2). In DAPPER, the primary efficacy assessment demonstrated that significantly more patients in the taper-to-placebo arm experienced a deterioration of 30% or greater on the 3TUG test than patients in the continuous-amifampridine arm. The assessment of this outcome was based on a threshold of 30% or greater deterioration in 3TUG time, which is clinically relevant based on the literature and input from clinical experts consulted for the CADTH review.[11] The use of the 3TUG test as the primary efficacy end point in DAPPER was appropriate; it is considered by the clinicians consulted by CADTH to be a clinically relevant tool and an appropriate means of assessing function in patients with LEMS. According to the clinical experts, the 3TUG test is also an appropriate component of assessing treatment response in patients with LEMS in clinic. Despite support from the experts consulted by CADTH for the use of the 3TUG test in clinic, the 3TUG test is not consistently used in routine assessments of patients with LEMS in the Canadian clinical setting. Differential use of the test may be attributed to heterogeneity in clinic resources, given that some clinics rely on neurological exams and do not have the capacity to do timed assessments or more comprehensive exams of patients' day-to-day function.

The secondary efficacy end point in DAPPER, the W-SAS, provided a global self-assessment that demonstrated a statistically significant increase in weakness in patients in the taper-to-placebo arm compared to those in the continuous-amifampridine arm; however, inference for this secondary outcome is limited, given that it was not adjusted for multiple comparisons. This prevents firm conclusions from being drawn. No MID for patients with LEMS was identified in the literature; however, the clinical experts consulted by CADTH determined that the results were clinically meaningful. The use of the W-SAS in DAPPER was similar to assessments of patients' subjective responses to treatment that are used in clinic. While DAPPER was a double-blind study, the use of a withdrawal enrichment strategy inherently introduced the possibility of unblinding because patients in the placebo arm were expected to experience deterioration prior to amifampridine being reinstated. This potential unblinding may have biased the subjective outcome results, such as those for the W-SAS, in favour of amifampridine.

Outcomes for CMAP, LEFS, and LEMS-related ADLs were reported descriptively, without performing formal statistical testing. As a phase II trial, DAPPER was not designed to test multiple outcomes and did not have a statistical testing framework.[12] Therefore, firm conclusions cannot be drawn based on the assessments of outcomes for CMAP, LEFS, and LEMS-related ADLs. However, the clinical experts consulted by CADTH determined that the results were clinically meaningful and supported the primary and secondary efficacy outcomes.

LEMS-related symptoms, HRQoL, and outcomes related to productivity were also important to patients, according to the input received for this review. However, these outcomes were not assessed in DAPPER. Thus, the efficacy of amifampridine with respect to LEMS-related symptoms, HRQoL, and productivity remain unknown.

Subgroup analyses based on LEMS type (paraneoplastic versus primary autoimmune) and age (pediatric versus adult patients) were not performed in DAPPER. LEMS is classified as either paraneoplastic or primary autoimmune. Both therapy and prognosis may differ depending on whether LEMS is paraneoplastic or primary autoimmune in origin. Patients

were excluded from DAPPER if they had a clinically significant or poorly controlled condition that, in the opinion of the study personnel, might have posed an unacceptable risk to them if they entered into the study. This criterion may partially explain the underrepresentation of patients (n = 1) with paraneoplastic LEMS observed in DAPPER. The underrepresentation of patients with paraneoplastic LEMS differs from the clinical setting, where approximately 50% to 60% of LEMS patients have the paraneoplastic type. Whether or not the treatment effect differs based on LEMS type (paraneoplastic versus primary autoimmune) remains unknown.

Amifampridine is indicated for patients with LEMS who were 6 years of age and older. DAPPER enrolled patients 18 years of age and older; patients ranged from 23 years to 83 years of age. Therefore, whether or not the treatment effect differs based on age group remains unknown. However, given the general mechanism of action, amifampridine is not expected to have differential impacts on efficacy across age groups, according to the clinical experts consulted for this review.

DAPPER used a withdrawal enrichment strategy. The study design and eligibility criteria led to a study population that consisted of patients who were treatment-experienced and responsive to amifampridine at baseline. Patients were required to have had at least 3 months of continuous treatment with amifampridine. According to the sponsor, this was intended to allow for stabilization and optimization of any physical conditioning, and to achieve a full treatment effect. Patients were required to be responsive to amifampridine, which was defined as being able to experience an unequivocal improvement in a LEMS-induced dysfunction within 15 minutes to 30 minutes after the first dose of amifampridine in the morning. According to the sponsor, this approach avoided the inclusion of patients whose LEMS may have improved or remitted over time. Collectively, these criteria led to a study population whose magnitude of treatment response may not be representative of the Canadian amifampridine-experienced population or generalizable to amifampridine-naive patients. While enrichment strategies such as these have been used in studies of rare disease populations, the trial design of DAPPER limits generalizability to all patients who may be eligible for treatment with amifampridine, as per the Health Canada indication.

In the DUKE study, the primary efficacy outcome of mean change from baseline in QMG score favoured the amifampridine treatment group compared to placebo. Treatment with amifampridine led to an improvement of –2.0 (SD = 2.16) in the mean change from baseline; the result was statistically significant (P = 0.015). Consistent with the 3TUG test results from DAPPER, the results of the QMG score in DUKE favoured the use of amifampridine. However, the QMG score is not considered an appropriate or relevant assessment tool for LEMS, according to the clinical experts consulted by CADTH. The QMG was designed for the MG population. Despite its use in the DUKE study and historical studies of LEMS, the QMG was not designed for LEMS assessment; further, it does not assess the body parts affected by LEMS. Results of the CMAP were aligned with those of the QMG, but it is unclear if this outcome was controlled for multiplicity. As a result, this needs to be considered for type I error. Assessments of swallowing time (P = 0.112) and walking time (P = 0.648) showed no difference in these outcomes between the treatment groups. Overall, the evidence from DUKE on the efficacy and safety of amifampridine is limited by concerns related to both internal and external validity; the quality of the evidence is low; and due to a lack of detail pertaining to the statistical methodology, a thorough critical appraisal of the study could not be conducted.

In the Oh (2009) study, the mean ± SE for the QMG score change was –2.36 ± 2.25 in the amifampridine group and 0.40 ± 1.14 in the placebo treatment group (P = 0.0223). However, as previously specified, the clinical experts consulted by CADTH agreed that the QMG score is not considered an appropriate or relevant tool for assessing LEMS. The mean ± SE for CMAP change was 1.79 ± 2.05 in the amifampridine group and –0.90 ± 1.78 in the placebo group (P = 0.0246). A clear description of the primary and secondary outcomes was not provided; therefore, results may need to be considered with regard to type I error.

McEvoy (1989) reported that the average resting, facilitated, and decrement CMAPs during the double-blind phase in the active drug treatment group were 5.1 ± 0.9 mV, 9.6 ± 0.8 mV, and 21.6 ± 2.2% in the arm and 3.2 ± 0.7 mV, 4.9 ± 0.9 mV, and 20.4 ± 2.6% in the leg. In the placebo group, these figures were 2.8 ± 0.6 mV, 7.6 ± 0.7 mV, and 28.6 ± 3.0% (P < 0.005) in the arm and 1.8 ± 0.4 mV, 3.4 ± 0.7 mV, and 25.8 ± 2.3% (P < 0.010) in the leg.

The Oh and McEvoy studies had limitations related to study design, including small sample sizes, lack of washouts period, and failure to control for multiplicity. These limitations limited the studies' limiting internal validity. Neither study provided sufficient detail regarding the methodological design or statistical analysis plan; therefore, a thorough critical appraisal was not possible. Insufficient detail limited CADTH's ability to fully discern generalizability to the Canadian population of patients with LEMS. It was unclear if any of the patients in Oh were amifampridine-naive. Both Oh and McEvoy included patients with paraneoplastic LEMS. However, the limitations of the studies prevent interpretation of the results.

## Harms

In DAPPER, AEs excluding LEMS-related signs and symptoms occurred in 5 patients (35.7%) in the continuous-amifampridine arm and in 12 patients (66.7%) in the taper-to-placebo arm. The most common AEs were abdominal discomfort and respiratory tract infection, each of which occurred in 2 patients (11.1%) in the taper-to-placebo arm. AEs attributed to LEMS-related signs and symptoms occurred in 2 patients (14.3%) in the continuous-amifampridine arm and in 6 patients (33.3%) in the taper-to-placebo arm. The most common AEs were decreased oxygen saturation (N = 3, 16.7%), muscle spasms (N = 2, 11.1%), and nausea (N = 2, 11.1%), which only occurred in patients in the taper-to-placebo arm. One patient (5.6%) in the taper-to-placebo arm experienced prolonged QT assessed through electrocardiogram and 1 patient (5.6%) in the taper-to-placebo arm experienced paresthesia. Seizures were not reported in DAPPER.

In DAPPER, 1 patient (5.6%) in the taper-to-placebo arm experienced an SAE of severe pneumonia. Two patients in the taper-to-placebo arm withdrew from treatment due to AEs attributed to LEMS-related signs and symptoms: decreased oxygen saturation (5.6%) and anxiety (5.6%). No deaths were reported during DAPPER.

The duration and design of DAPPER were limited. As a result, the study's results may not be a true reflection of the harms associated with amifampridine for all patients with LEMS. The patients included in DAPPER were not amifampridine-naive. They were required to be on a stable and optimized dose of amifampridine and meet a threshold of responsiveness to amifampridine at baseline. While DAPPER was the main source of harms evidence assessed by CADTH, Health Canada also used data from DUKE, the Retrospective Pharmacovigilance Reviews of long-term Compassionate Use Programs, and published medical literature.[21]

In DUKE, perioral tingling and digital paresthesia were reported in 4 of 14 patients while they were taking blinded amifampridine and in 8 of 22 patients while they were taking open-label amifampridine. A retrospective review of safety data conducted by the sponsor revealed that SAEs were reported in 3 patients. One patient treated with placebo experienced anxiety, respiratory difficulties, difficulty speaking, and chest discomfort. One patient randomized to amifampridine was hospitalized for muscle weakness about 1 week after completing the study, and 1 patient randomized to placebo died of pulmonary complications of lung cancer approximately 1 month after starting open-label treatment with amifampridine.

In the Oh (2009) study, paresthesia was reported in 2 patients treated with amifampridine. In the McEvoy (1989) study, 10 out of 12 patients experienced perioral or acral paresthesias after 30 minutes of administering amifampridine. After 10 months of treatment, 1 patient had a seizure after receiving a maximal dose of 100 mg of amifampridine.

## Conclusions

One phase II, double-blind, placebo-controlled withdrawal study (DAPPER; N = 32) of patients with LEMS demonstrated that continuous treatment with amifampridine resulted in less disability progression compared with patients whose amifampridine was withdrawn. In DAPPER, a greater proportion of patients in the taper-to-placebo arm (72.2%) exhibited a deterioration of 30% or greater on the 3TUG test compared to patients in the continuous-amifampridine arm (0%). The W-SAS provided a global self-assessment that demonstrated increased weakness among patients in the taper-to-placebo arm (mean = –2.4) compared to the continuous-amifampridine arm (mean = –0.2). However, caution is warranted when drawing firm conclusions due to lack of control for multiple comparisons. The effect of amifampridine on HRQoL and productivity was not evaluated in DAPPER and remains unknown. DAPPER was limited by the potential for unblinding and lack of generalizability to the amifampridine-naive patient population. The evidence available from the DUKE study was consistent with the clinical findings from DAPPER.

Evidence gaps for the reviewed studies include the use of amifampridine in amifampridine-naive patients, patients with paraneoplastic LEMS, and pediatric patients.

The harms data obtained from the body of evidence reviewed for the CADTH report are limited. Due to the duration and design of DAPPER, the harms reported may not be a true reflection of the harms associated with amifampridine for all patients with LEMS.

# Appendix 1: Literature Search Strategy

## Clinical Literature Search

| OVERVIEW | |
|---|---|
| Interface: | Ovid |
| Databases: | MEDLINE All (1946 to present)<br>Embase (1974 to present)<br>**Note:** Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid. |
| Date of Search: | November 3, 2020 |
| Alerts: | Weekly search updates until project completion |
| Study Types: | No filters used |
| Limits: | Publication date limit: None used<br>Humans<br>Language limit: No limits used<br>Conference abstracts: excluded |

| SYNTAX GUIDE | |
|---|---|
| / | At the end of a phrase, searches the phrase as a subject heading |
| MeSH | Medical Subject Heading |
| .fs | Floating subheading |
| exp | Explode a subject heading |
| * | Before a word, indicates that the marked subject heading is a primary topic;<br>or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings |
| # | Truncation symbol for one character |
| ? | Truncation symbol for one or no characters only |
| adj# | Requires terms to be adjacent to each other within # number of words (in any order) |
| .ti | Title |
| .ab | Abstract |
| .hw | Heading word; usually includes subject headings and controlled vocabulary |
| .kf | Author keyword heading word (MEDLINE) |
| .kw | Author keyword (Embase); keyword (CDSR) |
| .pt | Publication type |
| .mp | Mapped term |
| .rn | Registry number |
| .yr | Publication year |
| .jw | Journal title word (MEDLINE) |
| .jx | Journal title word (Embase) |
| freq=# | Requires terms to occur # number of times in the specified fields |
| medall | Ovid database code: MEDLINE All, 1946 to present, updated daily |
| oemezd | Ovid database code; Embase, 1974 to present, updated daily |
| cctr | Ovid database code; Cochrane Central Register of Controlled Trials |

| MULTI-DATABASE STRATEGY | |
|---|---|
| **#** | **Searches** |
| 1 | amifampridine/ |
| 2 | (ruzurgi* or amifampridine* or firdapse* or zenas* or nsc521760 or nsc 521760 or brn0110232 or "brn 0110232" or RU4s6E2G0J or "3,4-dap" or "3,4-dapp" or "3,4dap" or "3,4dapp").ti,ab,rn,ot,kf,nm. |
| 3 | ("3,4-diaminopyridine" or "3,4-pyridinediamine" or "4,5-diaminopyridine").ti,ab,kf,rn,nm. |
| 4 | lambert-eaton myasthenic syndrome/ |
| 5 | (lambert-eaton* or LEMS or myasthen*).ti,ab,kf. |
| 6 | 4 or 5 |
| 7 | 3 and 6 |
| 8 | 1 or 2 or 7 |
| 9 | 8 use medall |
| 10 | *amifampridine/ |
| 11 | (ruzurgi* or amifampridine* or firdapse* or zenas* or nsc521760 or nsc 521760 or brn0110232 or "brn 0110232" or "3,4-dap" or "3,4-dapp" or "3,4dap" or "3,4dapp").ti,ab,kw,dq. |
| 12 | ("3,4-diaminopyridine" or "3,4-pyridinediamine" or "4,5-diaminopyridine").ti,ab,kw. |
| 13 | eaton lambert syndrome/ |
| 14 | (lambert-eaton* or LEMS or myasthen*).ti,ab,kw. |
| 15 | 13 or 14 |
| 16 | 12 and 15 |
| 17 | 10 or 11 or 16 |
| 18 | conference abstract.pt. |
| 19 | conference review.pt. |
| 20 | 18 or 19 |
| 21 | 17 not 20 |
| 22 | 21 use oemezd |
| 23 | 9 or 22 |
| 24 | exp animals/ |
| 25 | exp animal experimentation/ or exp animal experiment/ |
| 26 | exp models animal/ |
| 27 | nonhuman/ |
| 28 | exp vertebrate/ or exp vertebrates/ |
| 29 | or/24-28 |
| 30 | exp humans/ |
| 31 | exp human experimentation/ or exp human experiment/ |
| 32 | or/30-31 |
| 33 | 29 not 32 |
| 34 | 23 not 33 |
| 35 | remove duplicates from 34 |

| CLINICAL TRIALS REGISTRIES | |
|---|---|
| ClinicalTrials.gov | Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials.<br>[Search – Ruzurgi (amifampridine) and Lambert-Eaton myasthenic syndrome] |
| WHO ICTRP | International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials.<br>[Search – Ruzurgi (amifampridine) and Lambert-Eaton myasthenic syndrome] |
| Health Canada's Clinical Trials Database | Produced by Health Canada. Targeted search used to capture registered clinical trials.<br>[Search – Ruzurgi (amifampridine) and Lambert-Eaton myasthenic syndrome] |
| EU Clinical Trials Register | European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.<br>[Search – Ruzurgi (amifampridine) and Lambert-Eaton myasthenic syndrome] |

### Grey Literature

| | |
|---|---|
| Search dates: | October 22, 2020 to October 29, 2020 |
| Keywords: | Ruzurgi (amifampridine) and Lambert-Eaton myasthenic syndrome] |
| Limits: | Publication years: No limits used |

Relevant websites from the following sections of the CADTH grey literature checklist, *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* (https://www.cadth.ca/grey-matters), were searched:

- Health Technology Assessments
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trials Registries
- Databases (free)
- Health Statistics
- Internet Search

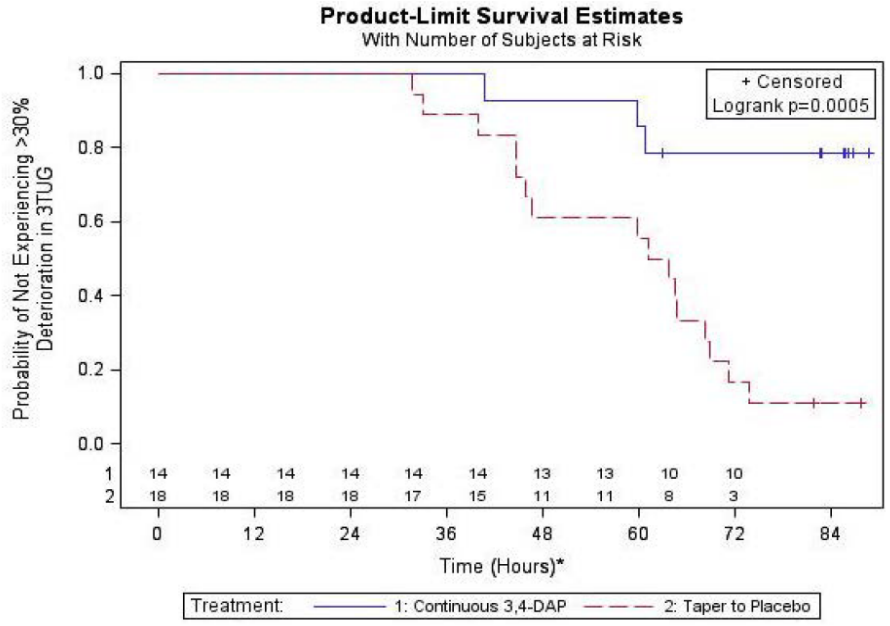
# Appendix 2: Excluded Studies

## Table 28: Studies Excluded From the CADTH Systematic Review

| Reference | Reason for exclusion |
|---|---|
| Clinical Study Report (supplement): JPC 3,4-DAP DUKE RCT Supplement [CONFIDENTIAL internal sponsor's report]. Princeton (NJ): Jacobus Pharmaceutical Company, Inc.; 2016.[24] | Study design |
| Wirtz PW, Verschuuren JJ, van Dijk JG, et al. Efficacy of 3,4-diaminopyridine and pyridostigmine in the treatment of Lambert-Eaton myasthenic syndrome: a randomized, double-blind, placebo-controlled, crossover study. *Clinical Pharmacology & Therapeutics.* 2009;86(1):44-48.[26] | Study design |
| Oh SJ, Claussen GG, Hatanaka Y, Morgan MB. 3,4-Diaminopyridine is more effective than placebo in a randomized, double-blind, cross-over drug study in LEMS. *Muscle Nerve.* 2009;40(5):795-800.[14] | Study design |
| Sanders DB, Massey JM, Sanders LL, Edwards LJ. A randomized trial of 3,4-diaminopyridine in Lambert-Eaton myasthenic syndrome. *Neurology.* 2000;54(3):603-607.[23] | Study design |
| McEvoy KM, Windebank AJ, Daube JR, Low PA. 3,4-Diaminopyridine in the treatment of Lambert-Eaton myasthenic syndrome. *New England Journal of Medicine.* 1989;321(23):1567-1571.[25] | Study design |

# Appendix 3: Detailed Outcome Data

## Figure 8: Kaplan-Meier Plot for Time to Experiencing a Deterioration in 3TUG of Greater Than 30%




* 0 hour is defined as the last dose of Day 2

3,4-DAP = 3,4-diaminopyridine; 3TUG = Triple-Timed Up-and-Go.

Note: Efficacy population.

Source: Clinical Study Report for JPC 3,4-DAPPER.[13]

## Table 29: CMAP: Blinded Reviewer-Approved Records (Efficacy Population)

| | DAPPER | | | |
|---|---|---|---|---|
| | Continuous amifampridine N = 14 | | Taper to placebo N = 18 | |
| **Muscle statistics** | **Measurement (mV)** | **% change from baseline[a]** | **Measurement (mV)** | **% change from baseline[a]** |
| **Final post-dose CMAP – blinded reviewer-approved records** | | | | |
| ADQ | | | | |
| N | 4 | 4 | 3 | 3 |
| Mean (SD) | 6.7 (4.11) | –6.3 (8.51) | 2.8 (1.80) | –35.2 (30.96) |
| Median (min, max) | 7.1 (1.3, 11.2) | –8.3 (–14.3, 5.6) | 2.3 (1.3, 4.8) | –28.9 (–68.9, –7.9) |
| APB | | | | |
| N | 4 | 4 | 9 | 9 |
| Mean (SD) | 6.0 (4.24) | 1.3 (20.63) | 3.1 (1.86) | –46.0 (17.81) |
| Median (min, max) | 5.6 (2.1, 10.7) | –1.2 (–19.8, 27.3) | 3.2 (0.4, 5.2) | –41.3 (–80.9, –28.0) |
| EDB | | | | |

| | DAPPER | | | |
|---|---|---|---|---|
| | Continuous amifampridine N = 14 | | Taper to placebo N = 18 | |
| N | 3 | 3 | 2 | 2 |
| Mean (SD) | 1.8 (1.38) | –28.2 (28.34) | 1.3 (1.34) | –48.9 (8.59) |
| Median (min, max) | 1.1 (0.9, 3.4) | –14.8 (–60.7, –9.0) | 1.3 (0.3, 2.2) | –48.9 (–55.0, –42.9) |
| ADQ | | | | |
| All muscle types | | | | |
| N | 11 | 11 | 14 | 14 |
| Mean (SD) | 5.1 (3.93) | –9.5 (21.57) | 2.8 (1.79) | –44.1 (19.30) |
| Median (min, max) | 3.4 (0.9, 11.2) | –9.5 (–60.7, 27.3) | 2.3 (0.3, 5.2) | –42.1 (–80.9, –7.9) |

ADQ = abductor digiti quinti muscle; APB = abductor pollicis brevis muscle; CMAP = compound muscle action potential; EDB = extensor digitorum brevis muscle; mV = millivolts; SD = standard deviation.

Note: Last available post-dose CMAP during stage 2. A positive percentage change represents an improvement, and a negative percentage change represents a deterioration in CMAP.

[a] Baseline is the average of time-matched observations at post-dose on days 1 and 2 in stage 1.

Source: Clinical Study Report for JPC 3,4-DAPPER.[13]

# Appendix 4: Description and Appraisal of Outcome Measures

## Aim

To describe the following outcome measures and review their measurement properties (validity, reliability, responsiveness to change, and MID):

- 3TUG
- W-SAS
- LEFS
- LEMS-related ADLs
- QMG score

### Table 30: Summary of Outcome Measures and Their Measurement Properties

| Outcome measure | Type | Conclusions about measurement properties | MID |
|---|---|---|---|
| 3TUG | The 3TUG test consists of attempting to walk normally and completing 3 consecutive laps. The 3TUG time is the average of the 3 lap times.[11] | **Validity**<br>The Spearman correlation showed a strong negative correlation between 3TUG time and total LEFS score.[27]<br>**Reliability**<br>Test-rest reproducibility: the CP for agreement in time-matched observations on consecutive days is 0.93 (95% CI, 0.82 to 0.99) for an acceptable range of ≤ 20%, and 0.67 (95% CI, 0.54 to 0.81) for an acceptable range of ≤ 10%.[27]<br>Inter-rater reliability: the CP for agreement between unblinded and blinded observers for the same 3TUG test was 1.00 (95% CI, 0.92 to 1.00) for an acceptable range of ≤ 20%, and 1.00 (95% CI, 0.92 to 1.00) for an acceptable range of ≤ 10%.[27] | A MID for patients with LEMS was not identified in the literature. |
| W-SAS | The W-SAS has 7 categories with numerical values that allow a participant to rank weakness along a continuum from “much weaker” (–3) to “much stronger” (+3).[27] | Not identified from the literature. | Not identified from the literature. |
| LEFS | The LEFS consists of 20 items, each with a maximum possible score of 4. The total possible score of 80 indicates a high functional level. The scale is 1 | **Validity**<br>*Construct Validity*<br>The correlations between the LEFS scores and the SF-36 physical | The MDC is ± 9 scale points (90% CI). The MCID is approximately 9 scale points. |

| Outcome measure | Type | Conclusions about measurement properties | MID |
|---|---|---|---|
| | page, can be filled out by most patients in less than 2 minutes, and is scored by tallying the responses for all of the items. | function subscale and physical component summary scores were *r* = 0.80 (95% lower limit CI = 0.73) and *r* = 0.64 (95% lower limit CI = 0.54). The correlation between the LEFS scores and the SF-36 mental component summary scores was *r* = 0.30 (95% lower limit CI = 0.14).[22]<br>**Reliability**<br>Internal consistency was alpha = 0.96 (N = 107). Test-retest reliability estimates were *R* = 0.86 (95% lower limit CI = 0.80) for the entire sample (n = 98) and *R* = 0.94 (95% lower limit CI = 0.89) for the subset of patients with more chronic conditions (n = 31).[22] | The potential error associated with a LEFS score at a given point in time is ± 5.3 scale points on the 80-point scale (90% CI).[22]<br>No MID was identified for patients with LEMS. |
| LEMS-related ADLs | This is a 6-item, patient-reported outcome measure that is scored from 1 (worst) to 4 (best). | Not identified from the literature. | Not identified from the literature. |
| QMG score | The QMG assessment is a 13-item, direct physician scoring system that quantifies disease severity based on impairments of body functions and structures. The total QMG score ranges from 0 to 39, where higher scores indicate greater disease severity. | **Validity**<br>Construct validity was assessed through correlations with the manual muscle test (r = 0.69) and the myasthenia muscle score (r = 0.87).<br>**Reliability**<br>Internal consistency assessed using the Cronbach alpha value was 0.74 for the QMG, demonstrating an acceptable threshold. [28]<br>Test-retest reliability was studied in 209 stable patients assessed 2 weeks apart. The intraclass correlation coefficient for the total scores was 0.88 (95% CI, 0.85 to 0.91). [28]<br>**Responsiveness**<br>The QMG has demonstrated responsiveness to change in various clinical trials (IVIg, cyclosporine), where patients showed statistically significant improvement in QMG after treatment compared to the placebo group. | A MID has not been identified in patients with LEMS.<br>A MID of 2.6 points in patients with MG was determined in the original QMG publication.[29] |

3TUG = Triple-Timed Up-and-Go; ADL = activities of daily living; CI = confidence interval; CP = coverage probability; IVIg = intravenous immunoglobulin; LEFS = Lower Extremity Functional Scale; LEMS = Lambert-Eaton myasthenic syndrome; MDC = minimal detectable change; MCID = minimal clinically important difference; MG = myasthenia gravis; MID = minimal important difference; QMG = quantitative myasthenia gravis; r = correlation coefficient; R = reliability; SF-36 = Short Form (36) Health Survey;
W-SAS = self-assessment of LEMS-related weakness.

### Triple-Timed Up-and-Go Test

The 3TUG test is an observable measure of disease severity. It is used to assess the potential effect on the timed up-and-go of neuromuscular fatigue or facilitation, which are characteristic of LEMS. The 3TUG test consists of 3 laps performed as follows: the patient begins seated in a standard 18-inch-high, straight-backed armchair. Three metres from the front legs of the chair, the floor is marked with a line of coloured tape, and the centre of the line is marked with an "X." Patients are instructed to get up from the chair, walk to the line at their normal pace, step on the X, turn around, walk back to the chair, turn around, and sit down. This is repeated 3 times without rest. Each lap ends when the patient's back contacts the chair back and the patient is either instructed to begin the next lap or informed that the test is complete. The 3TUG time is the average of the 3 lap times.[11]

In the DAPPER study, the 3TUG test results obtained 2 hours after the last dose during the withdrawal period were used for the analysis of the primary outcome. The categories of 3TUG performance used in the sponsor's submission during stage 2 of the trial were assigned as described in Table 31.

## Table 31: Category of 3TUG Performance in DAPPER

| Category of performance | Estimate |
|---|---|
| Improvement | A: > 30% faster |
| No change | B: No change; i.e., 30% slower to 30% faster |
| Deterioration | C: > 30% to 50% slower |
| | D: > 50% to 100% slower |
| | E: > 100% to 200% slower |
| | F: > 200% slower |
| | G: Cannot perform 3TUG |

3TUG = Triple-Timed Up-and-Go.

Source: Clinical Study Report for JPC 3,4 DAPPER.[13]

#### *Measurement Properties*

Two published studies reported on the validity and reliability of the 3TUG test.[11,27] One study had 3 independent observers[11] and the second had 2 independent observers.[27]

Construct validity was established through correlation with other measures of LEMS-specific disability and by assessing responsiveness to patient- and provider-reported measures of disease severity. The Spearman correlation showed a strong negative correlation between the 3TUG time and total LEFS score before the reinstitution of amifampridine in the group continuing on amifampridine (r = –0.64; P = 0.02) and in those who were withdrawn from amifampridine (r = −0.64; P = 0.01).[27] The results here selectively describe the construct only in patients who were not being administered amifampridine at the time. They do not describe the results after the reinstitution of amifampridine.

Intra-rater reproducibility and inter-rater agreement for the 3TUG were assessed in 25 control patients, 24 patients with non-LEMS neuromuscular disease, and 12 patients with LEMS. The enrolled patients first performed 3 laps without timing to minimize the effect of learning. They then participated in a timed trial (test 1), a 5-minute rest period, and a second timed trial (test 2).[11]

The a priori acceptable range was a difference of less than 20% in 3TUG times and a CP of greater than or equal to 0.90 confirmed agreement. Intra-rater (test-retest) reproducibility in 25 patients showed that the mean percentage difference between 2 tests among 3 observers was 1.54, and none of the pairs exceeded a 20% difference, resulting in a CP of 1.0 and demonstrating agreement. Of the 24 patients with a non-LEM neuromuscular disease, the mean percentage difference between the 2 tests among the 3 observers for the 72 pairs was 1.90, and none of the differences exceeded 20%, resulting in a CP of 1.0 and demonstrating agreement. Among the 12 LEM patients, the mean 3TUG time on day 0 was 9.37 seconds; on day 1, it was 8.96 seconds. The difference exceeded 10% in 5 of 24 pairs and exceeded 20% in 2 pairs, resulting in a CP of 0.92, which is above the pre-established threshold of 0.90 for acceptable agreement.[11]

The inter-rater reliability showed that the average difference in 3TUG times measured did not exceed 20% (or even 10%) for any of the pairs, resulting in a CP of 1.0 in all groups.[11] The CPs for agreement between unblinded and blinded observers were 1.00 (95% confidence interval [CI], 0.92 to 1.00), for an acceptable range of less than or equal to 20%, and 1.00 (95% CI, 0.92 to 1.00), for an acceptable range of less than or equal to 10%.[27] Therefore, the scale demonstrates a high level of inter-rate agreement.

### *Minimal Important Difference*

No MID for the 3TUG measure was identified.

## Self-Assessment of LEMS-Related Weakness

The W-SAS is a single-item, global self-assessment scale for evaluating LEMS-related weakness. It is a 7-category scale, with numerical values where weakness is ranked along a continuum from “much much weaker” (–3) to “much much stronger” (+3).[27] The patient is asked to place an “X” in the box best describing how they feel. “Much much weaker” is on the left end of the scale, while “much much better” is on the right end. “About the same” (0) is in the middle. The tool was administered 3 times daily at the estimated peak time of drug effect.

No studies assessing the validity or reliability of the W-SAS were identified for patients with LEMS.[27] No MID was identified in the literature search.

## Lower Extremities Functional Scale

The LEFS is a 20-item, patient-reported outcome measure commonly used to assess mobility in patients with orthopedic conditions. The scale is 1 page and items are rated on a 5-point scale from 0 (extreme difficulty or inability to perform the activity) to 4 (no difficulty). The total possible score is 80, which indicates a high functional level. One hundred and seven patients with lower-extremity musculoskeletal dysfunction were administered the LEFS.[22] The scale was initially developed for patients with lower-extremity musculoskeletal dysfunction, including orthopedic conditions, and was revised to include a broader spectrum of disorders; some items of the scale could have been removed due to floor effects. The validity and reliability of the scale in patients with LEMS was not identified from literature.

### *Measurement Properties*

In patients with lower-extremity musculoskeletal dysfunction, the construct validity was established using the SF-36 as a comparison scale. A 7-point prognostic rating scale examined the validity and sensitivity to change. Two blinded orthopedic physical therapists

performed an independent prognostic rating on each patient; these were subsequently averaged. Correlation between the LEFS scores and the SF-36 subscale and component summary scores was estimated using Pearson correlation coefficients and 95%, 1-sided, lower limit CIs. Correlations between the LEFS scores and the SF-36 physical function subscale and physical component summary scores were $r = 0.80$ (95% lower limit CI = 0.73) and $r = 0.64$ (95% lower limit CI = 0.54), respectively. The correlation between the LEFS scores and the SF-36 mental component summary scores was $r = 0.30$ (95% lower limit CI = 0.14).[22]

Internal consistency was measured using the alpha coefficient. A type 2,1 intraclass correlation coefficient was used to estimate test-retest reliability. Test-retest reliability was estimated over a 24-hour to 48-hour period using the entire patient population. The reliability of the LEFS score was also quantified using the SE of measurement.[22]

Internal consistency was alpha = 0.96 (N = 107). Test-retest reliability estimates were $R = 0.86$ (95% lower limit CI = 0.80) for the entire sample (n = 98) and $R = 0.94$ (95% lower limit CI = 0.89) for a subset of patients with more chronic conditions (n = 31).[22]

### *Minimal Important Difference*

The MID is ± 9 scale points.[22]

The validity and reliability of the LEFS in patients with LEMS was not identified from the literature.

## LEMS-Related Activities of Daily Living

LEMS-related ADLs, used as a functional measurement in the pivotal trial submitted by the sponsor, is a 6-item, patient-reported outcome measure. The outcomes were scored from 1 (worst) to 4 (best) and included toileting and bathing, dressing, eating and drinking, sit-to-stand, grooming, and bed mobility.

No studies describing the validity, reliability, or MID for the LEMS-related ADLs were found in literature.

## Quantitative Myasthenia Gravis Score

The QMG score is a 13-item scale developed to help physicians assess patients with MG. Each parameter is measured on a 0- to 3-point scale (total score range = 0 to 39). The QMG is composed of the following items: ocular (2 items), facial (1 item), bulbar (2 items), gross motor (6 items), axial (1 item), and respiratory (1 item). According to a 2000 publication by the Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America, the QMG score was recommended for use in all prospective MG clinical trials for evaluating treatment-related clinical change.[30]

### *Measurement Properties*

The QMG assesses relevant impairments of body functions and structures. Construct validity has been studied through demonstrations of correlations with other measures used to assess MG. Test-retest reliability was studied in 209 stable patients assessed 2 weeks apart. The intraclass correlation coefficient for the total scores was 0.88 (95% CI, 0.85 to 0.91).[28,31] Internal consistency assessed using the Cronbach alpha value was 0.74 for the QMG, demonstrating an acceptable threshold.[28,31]

A longitudinal study of 53 patients with an average of 186 days between visits determined that the difference in QMG score was significantly higher among those who improved (based on the physician's impression of change) than in those who remained stable.[32]

The QMG has demonstrated responsiveness to change in various clinical trials (IVIg, cyclosporine), where patients showed statistically significant improvement in QMG after treatment compared to the placebo group.[33]

Studies validating the use of the QMG score in patients with LEMS were not identified in the literature.

*Minimal Important Difference*

For patients with MG, the QMG score uses a MID of 2.6 points. There are no studies to support the use of this MID in patients with LEMS.

## Table 32: Quantitative Myasthenia Gravis Scale

| Test Items Weakness | None | Mild | Moderate | Severe |
|---|---|---|---|---|
| Double vision on lateral gaze **right** or **left** (circle one) | 61 | 11–60 | 1–10 | spontaneous |
| Ptosis (upward gaze) | 61 | 11–60 | 1–10 | spontaneous |
| Facial muscles | normal lid | complete, weak, some resistance | complete, without resistance | incomplete |
| Swallowing 4 oz. water (½ cup) | normal | Minimal coughing or throat clearing | severe coughing/ choking or nasal regurgitation | cannot swallow (test not attempted) |
| Speech following counting aloud from 1 to 50 (onset of dysarthria) | none at #50 | dysarthria at #30–49 | dysarthria at #10–29 | dysarthria at #9 |
| Right arm outstretched (90° sitting) | 240 | 90–239 | 10–89 | 0–9 |
| Left arm outstretched (90° sitting) | 240 | 90–239 | 10–89 | 0–9 |
| Vital capacity (% predicted) | ≥80% | 65–79% | 50–64% | <50% |
| Right hand grip (kg) | | | | |
| male | ≥45 | 15–44 | 5–14 | 0–4 |
| female | ≥30 | 10–29 | 5–9 | 0–4 |
| Left hand grip (kg) | | | | |
| male | ≥35 | 15–34 | 5–14 | 0–4 |
| female | ≥25 | 10–24 | 5–9 | 0–4 |
| Head lifted (45° supine) | 120 | 30–119 | 1–29 | 0 |
| Right leg outstretched (45° supine) | 100 | 31–99 | 1–30 | 0 |
| Left leg outstretched (45° supine) | 100 | 31–99 | 1–30 | 0 |

[a]Total QMG score range 0–39.

QMG = quantitative myasthenia gravis;

Reprinted from Ann N Y Acad Sci., vol 841, Barohn RJ et al. Reliability testing of the quantitative myasthenia gravis score. Pages 769-772, Copyright 1998 (licensed content date, 2006), with permission from John Wiley and Sons.[34]

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