Amifampridine Phosphate (Firdapse) Is Effective in a Confirmatory Phase 3 Clinical Trial in LEMS

Perry Shieh, MD, PhD, Khema Sharma, MD,† Bruce Kohrman, MD,‡ and Shin J. Oh, MD§*

Objective:

To assess tolerability and efficacy of amifampridine phosphate versus placebo for symptomatic treatment of Lambert–Eaton Myasthenic Syndrome (LEMS).

Methods:

This phase 3 randomized, double-blind, placebo-controlled withdrawal trial in 26 adults with LEMS compared efficacy of amifampridine phosphate versus placebo over a 4-day period. The primary endpoints were quantitative myasthenia gravis score (QMG) and subject global impression, and the secondary endpoint was Clinical Global Impression–Improvement. The exploratory endpoints were 3TUG (timed up and go) test and QMG limb domain score. All participants had been receiving amifampridine phosphate (30–80 mg/d divided into 3 or 4 doses daily) in an expanded access protocol and had been titrated to the optimal dose and frequency for at least 1 week before randomization into the current study. After completion of assessments after 4 days of double-blind treatment, patients had the option to return to open-label amifampridine phosphate. The efficacy endpoints were mean changes from baseline in the various evaluation parameters.

Results:

Amifampridine phosphate (n = 13) demonstrated significant benefit in QMG and subject global impression compared with placebo (n = 13) at 4 days. Other measures of efficacy, including Clinical Global Impression–Improvement, 3TUG, and QMG limb domain score also improved. The most common "adverse events" in the placebo group were muscle weakness (n = 5) and fatigue (n = 4), as expected from withdrawal of amifampridine phosphate, whereas only back pain (n = 1), pain in extremity (n = 1), and headache (n = 1) were reported in amifampridine phosphate group.

Conclusions:

This phase 3 randomized, double-blind, placebo-controlled withdrawal trial in adults with LEMS provided class I evidence of efficacy of amifampridine phosphate as symptomatic treatment in LEMS.

Lambert–Eaton myasthenic syndrome (LEMS) is a rare autoimmune neuromuscular disease caused by autoantibodies directed against type P/Q voltage-gated calcium channels (VGCC) located on the presynaptic membrane of the neuromuscular junction.[1,2] VGCC antibodies inhibit the entry of calcium into the nerve, impairing the release of acetylcholine from nerve terminals into the synapse, resulting in a loss of neuromuscular transmission.

Clinically, LEMS is characterized by proximal muscle weakness, fatigability, and autonomic dysfunction (eg, impotence, dry mouth, and constipation).[3] The classic triad includes proximal weakness, hyporeflexia, or areflexia, and cholinergic dysautonomia (dry mouth, impotence, and orthostatic hypotension).

Current approved treatment of LEMS is limited to guanidine, which acts by increasing transmitter release from presynaptic terminals, but it may cause bone marrow suppression and nephrotoxicity.[4] Cholinesterase inhibitor confers little benefit in LEMS, although they are sometimes used in combination with guanidine.[4]

As the safer potassium blockers, 4-aminopyridine (4-AP) and 3,4 diaminopyridine (DAP) have been introduced to treat LEMS;[5,6] 4-AP has proven to be less effective

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and has a narrow therapeutic margin, with many neurologic side effects, including seizures. On the other hand, 3,4 DAP has been shown to be more potent in improving neuromuscular transmission and less epileptogenic than 4-AP.[7]

Since 1982, the efficacy and safety of 3,4 DAP in LEMS treatment has been consistently well documented in multiple case reports and one open trial in more than 70 cases.[8] Moderate to marked functional improvement was seen in patients receiving 3,4 DAP at doses of 20–80 mg/d in 4 randomized trials (N = 7–26 patients) over 3–8 days.[9-12]

Amifampridine phosphate (Firdapse) is the name of the nonproprietary salt form of the active ingredient for 3,4 DAP. Amifampridine phosphate has superior stability compared with the 3,4 DAP base and can be stored at room temperature[13] and was approved as the first-line therapy in the European Union for the treatment of patients with LEMS in 2009.[14]

Efficacy and safety of amifampridine phosphate as symptomatic treatment for LEMS was reported in a phase 3 multicenter clinical trial in 2016.[15] This study is designed as the second phase 3 study to confirm the efficacy and tolerability of amifampridine phosphate compared with placebo in patients with LEMS. This is to satisfy 2 adequate and well-controlled studies, the required criteria for new drug approval by the US Food and Drug Administration.

METHODS

Study Design

This randomized, double-blind, withdrawal, controlled trial was conducted at 3 sites in the United States. All patients enrolled in this study had already been receiving open-label amifampridine phosphate in an Expanded Access Program (EAP), on a stable dose, for at least 1 week (Fig. 1). All patients volunteered to participate in this study after learning about this study through the EAP. After baseline assessments were obtained on study day 0, with patients on open-label amifampridine phosphate at their usual dosing schedule, they were assigned to placebo or amifampridine phosphate (1:1) according to a randomization schedule. Blinded study medication was taken on days 1 through 3. On day 4, a dose of blinded study medication was administered in the clinic, and assessments were performed 45 minutes after a dose of medication, at a time that peak blood levels would be expected. After completion of the study, patients were eligible to return to the EAP with open-label amifampridine phosphate.

Patient Selection

Inclusion and exclusion criteria in this study were identical with those used for the first phase 3 study.[15] Inclusion criteria were ambulatory participants aged 18 years and older with LEMS. The diagnosis of LEMS was made when patients had acquired proximal muscle weakness and at least 1 of the following: positive anti-P/Q type VGCC antibody test or compound muscle action potential (CMAP) that increased ≥100% after maximum voluntary contraction of the tested muscle (postexercise facilitation) in the abductor digiti muscle.[2,15,16] Concomitant medications, cholinesterase inhibitors, or oral corticosteroids were permitted as long as the dose was stable for at least 7 and 30 days, respectively, before randomization and throughout the study. Females of childbearing potential must have practiced effective, reliable contraceptive regimen during the study. Patients with cancer were required to have completed anticancer treatment ≥3 months before study entry. Exclusion criteria included clinically significantly prolonged interval on ECG within the previous 12 months, seizure disorder, active brain metastases, inability to ambulate, pregnant or lactating females, and inability to discontinue immunomodulatory treatment (eg, mycophenolate, azathioprine, and cyclosporine) within 3 weeks before study entry.
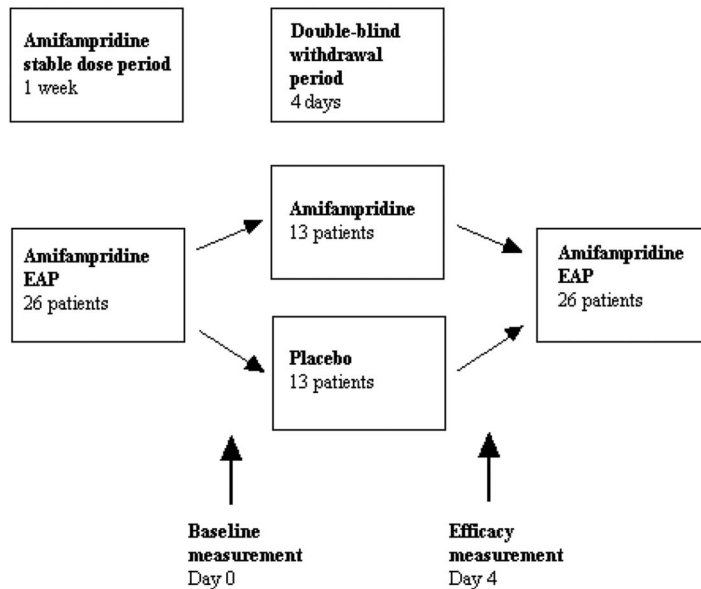
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FIGURE 1. Study design.

Standard Protocol Approvals, Registrations, and Patient Consents

The research protocol and all study documents were approved by 3 institutional review boards. Written informed consent was obtained before participants entering the study (Clinical Trial identifier, double-blind NCT02970162).

Study Objectives

The primary objectives of the study were to assess the clinical efficacy of amifampridine phosphate compared with placebo in patients with LEMS based on improvement in subject global impression (SGI) and quantitative myasthenia gravis (QMG) score, and to confirm the tolerability of amifampridine phosphate by adverse event (AE) reports.[15,17,18] The secondary efficacy variable was the Clinical Global Impression–Improvement (CGI-I) score.[19] Exploratory efficacy variables were to evaluate the clinical efficacy of amifampridine phosphate as measured by triple timed up and go (3TUG) and by QMG limb domain (LD) score.[15,17,20]

Procedures

The QMG is a physician-rated evaluation consisting of 13 assessments mainly designed for clinical trials in patients with myasthenia gravis. The 13 individual assessment scores are totaled to obtain a QMG score that provides a quantitative assessment of muscle function For QMG assessment, lower scores reflect better muscle function.[17]

The SGI is a 7-point scale on which patients rate their global impression of the effects of a study treatment (1 = terrible to 7 = delighted) on their LEMS symptoms. For SGI assessment, higher ratings reflect a higher level of patient satisfaction.[18]

Exploratory endpoints include 3 TUG test and QMG-LD score.[17,20] The TUG test is a functional mobility test that requires a patient to stand up from a straight-backed armchair (18-in seat height), walk 3 m, turn around, walk back, and sit down in the chair. An individual performs the test 3 times without pause (3TUG), and the measurement is the time required to complete all 3 of the repetitions. To remove all potential "rater bias" from the test, a calibrated electronic mat was used to measure the position and force of the subject's feet on the mat, and the force of the standard 18-in chair on the mat, at a data acquisition rate of 120 samples per second (intervals of approximately 8 ms). These high-resolution measurements enable the detection of the subject's start and end

times to a resolution of ±8 ms. A clinically significant change in gait for this test is an increase in time of more than 20%; this is incorporated into the endpoint and used for the definition of a responder.[21,22]

QMG-LD score is a total sum of right and left arm and leg raising maneuvers in QMG. The QMG-LD score is selected to assess the most prominent finding in LEMS, proximal muscle weakness.[17]

Efficacy Assessments

The coprimary efficacy assessments were the changes from baseline to day 4 in SGI and total QMG scores.[15,17,18] Secondary and exploratory assessments were CGI, at least a 20% change in average 3TUG time and change from baseline (CFB) of the QMG-LD score.[19-22]

Safety Assessments

Safety was evaluated by the incidence of AEs and changes in vital signs.

Statistical Analyses

The study is powered with respect to the coprimary efficacy endpoints of the study. For CFB in QMG scores, a between-treatment difference of −3.5 and a SD of at most 3, a sample size of at least 24 subjects will provide power of at least 80% for a 0.05 level 2-sided test. Similarly, for CFB in SGI scores, a between-treatment difference of −2.1 and a SD of at most 2, a sample size of at least 26 subjects will provide power of 80% for a 0.05 level 2-sided test. Thus a total sample size of 26 subjects, equally randomized to 2 treatment sequences, will provide power of at least 80% for each of the 2 coprimary endpoints.

Two analysis populations were planned for this study. The safety population included all participants who received at least 1 dose of study medication. The intent to treat population included all participants randomized into the study. The efficacy analyses were conducted using the intent to treat population. All safety analyses were conducted using the safety population, and summary statistics for the QMG days 0 and 4 assessments and the corresponding CFB were determined. The CFB for SGI and QMG were analyzed by fitting a fixed-effects linear model to the data with CFB as the response. The model included terms for treatment, SGI score and QMG score of the respective individual domain, or sum of these 4 domains, as applicable, at baseline. A comparison of the least square (LS) mean values was conducted to evaluate the treatment effect for each of these parameters. LS mean values or odds ratios and 95% confidence intervals (CIs) are presented for statistical models, as appropriate. Statistical testing was performed at the 0.05 level using 2-tailed tests. For the 3TUG testing, the proportion of patients meeting the criteria for the 20% or higher increase in time to complete was evaluated using a 2-sided Fisher exact test.

RESULTS

Participants

A total of 26 participants from 3 centers in the United States were enrolled in the study (Table 1). Most of the participants were non-Hispanic or Latino (21 [80.8%]) white and 10 (38.5%) participants were male. There was one African American. Overall mean (SD) participant age was 54.2 (12.30) years and body mass index was 29.4 kg/m².

Twenty-four patients had postexercise facilitation ≥100%. VGCC antibody was positive in 23 patients. These characteristics were similar between-treatment groups. *P* values between amifampridine and placebo groups for each category are >0.05. The mean total daily dose of amifampridine phosphate was also comparable in the 2 treatment groups before randomization. Cancer was present in 4 amifampridine phosphate group and 2 placebo group.

Efficacy Evaluation

The mean (±SD) baseline SGI scores were comparable for amifampridine phosphate (6.1 ± 0.86) and placebo groups (5.3 ± 1.65) (Table 2). The primary efficacy analysis demonstrated a significant LS mean difference for SGI in favor of amifampridine

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TABLE 1. Demographic and Baseline Characteristic Data

	Amifampridine	**Placebo**	**Overall**
N	13	13	26
Ethnicity; Non-Hispanic/Hispanic	9/4	12/1	21/5
Sex: men/women	6/7	4/9	10/16
Mean age (range)	54.9 (33–71)	53.4 (31–75)	54.2 (31–75)
BMI, kg/m^2, mean (range)	28.4 (24.2–34.9)	30.4 (20.6–40.1)	29.4 (20.6–40.1)
PEF $\geq$100%	12	12	24
Positive VGCC antibody	11	12	23
Cancer	4	2	6
Amifampridine dose per day at study entry	60.0 ± 19.6	63.1 ± 18.99	61.5 ± 18.60

All 26 patients had either positive VGCC antibody test or PEF $\geq$100%. *P* values between amifampridine and placebo groups for each category are >0.05.

BMI, body mass index; PEF, postexercise facilitation.

phosphate (-0.3 vs. -2.9, $P = 0.0003$, 95% CI, 1.53–4.38), compared with placebo. Baseline QMG total scores were similar in the amifampridine phosphate (7.8 ± 4.20) and placebo groups (7.9 ± 4.92). A significant LS mean difference for QMG total score in favor of amifampridine phosphate (0.7 vs. 7.1, $P = 0.0004$, 95% Cl, -0.78 to -3.29) was found (Fig. 2). A sensitivity analysis with a permutation test resulted in the same statistical interpretation (statistical significance ($P = 0.0006$) in favor of amifampridine phosphate and confirmed that the mixed model was used appropriately in statistical analysis for these endpoints. Thus, 2 primary endpoints in favor of amifampridine phosphate were met.

The analysis of CGI-I at day 4 showed that the mean scores were lower (improvement) for amifampridine phosphate (3.8) compared with placebo (5.5), a difference that was statistically significant ($P = 0.002$), indicating that the secondary endpoint of this study is also met.

The analysis of exploratory items showed that 3TUG tests and QMG-LD score also met the endpoints of this study. In terms of 3TUG tests, the proportion of patients with a $\geq$20% increase in 3TUG average time was statistically significantly higher ($P = 0.0112$) in the placebo group [8/13 (61.5%)], compared with amifampridine phosphate [1/13 (7.7%)]. For QMG-LD score, the treatment differences

in LS mean values was 3.29 (Fig. 2). This difference was statistically significant ($P < 0.0001$) in favor of amifampridine phosphate. On further analysis of other 9 QMG items, the forced vital capacity (FVC) and head lift to 45 degrees showed a statistically significant difference in favor of amifampridine phosphate [$P = 0.005$ (-1.42 to -0.28) for FVC; $P = 0.0022$ (-1.47 to -0.37) for head lift] (Fig. 2). The other 7 items reflecting ocular, bulbar, and distal limb function did not show any significant difference between amifampridine phosphate and placebo.

Safety Evaluation

During the 4-day double-blind period, only 3 patients (23.08%) in amifampridine phosphate group reported an AE of either back pain (n = 1), pain in extremity (n = 1), or mild headache (n = 1). In the placebo group, the most common AEs were muscle weakness (n = 5), fatigue (n = 4), and dry mouth, asthenia, feeling hot, limb discomfort, muscle spasm, and balance disorder (n = 2 each), associated with the return of LEMS symptoms. Most of the AEs were of mild to moderate intensity, except for dry mouth, asthenia, and muscle weakness, which were of severe intensity. There were no clinically relevant changes in observed or CFB vital sign values. No patients were discontinued from the double-blind study.

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DISCUSSION

The efficacy of amifampridine phosphate as symptomatic treatment in patients with LEMS was confirmed in this study. Patients who received placebo had statistically significant worsening of muscle function measurements compared with patients who remained on amifampridine phosphate. In this randomized placebo-controlled withdrawal study, the coprimary endpoints SGI and QMG were unchanged from baseline after 4 days of amifampridine phosphate but worsened significantly from baseline to day 4 in those patients randomized to placebo. The treatment difference between the baseline and day 4 for the 2 regimens was also noted because 5 of 13 placebo-treated patients reported muscular weakness as an AE.

Furthermore, the QMG scores for the LDs, FVC, and head lift to 45 degrees were significantly worsened with placebo, underscoring the efficacy of amifampridine phosphate.

Since LEMS does not frequently affect ocular, facial, bulbar or distal limb muscles, it was not surprising that these QMG subscores were not significantly different in those receiving placebo compared with amifampridine.

The secondary efficacy endpoint, CGI-I scores at day 4, was significantly lower in the amifampridine group than that observed in the placebo group, indicative of better outcome. Evaluation of exploratory efficacy endpoints, including 3TUG, also demonstrated that amifampridine phosphate was having a positive effect on leg function. A

TABLE 2. Full Analysis Scores at Baseline and on Day 4 in the Primary, Secondary, and Exploratory Endpoints

	Baseline, N = 13	Day 4, N = 13
Primary endpoints		
SGI		
Amifampridine	6.1 ± 0.86	5.8 ± 0.90
Placebo	5.3 ± 1.65	2.4 ± 1.76
P value (95% CI)	0.0003 (1.53 to 4.38)	
QMG		
Amifampridine	7.8 ± 4.20	8.5 ± 5.43
Placebo	7.9 ± 4.94	15.0 ± 5.90
P value (95% CI)	0.0004 (−9.78 to −3.29)	
Secondary endpoints		
CGI-I		
Amifampridine	NA	3.8 ± 0.80
Placebo	NA	5.5 ± 1.27
P value	0.0020	
Exploratory endpoints		
3TUG*		
Amifampridine	NA	1 (7.7)
Placebo	NA	8 (61.5)
P value	0.0112	
QMG-LD score		
Amifampridine	3.9 ± 3.23	4.5 ± 2.90
Placebo	3.8 ± 3.34	7.5 ± 2.99
P value (95% CI)	0.0010 (−5.09 to 1.49)	

MBS, most bothersome symptom; TUG, timed up and go.
*Number and proportion of patients who had ≥20% increase in 3TUG average time.

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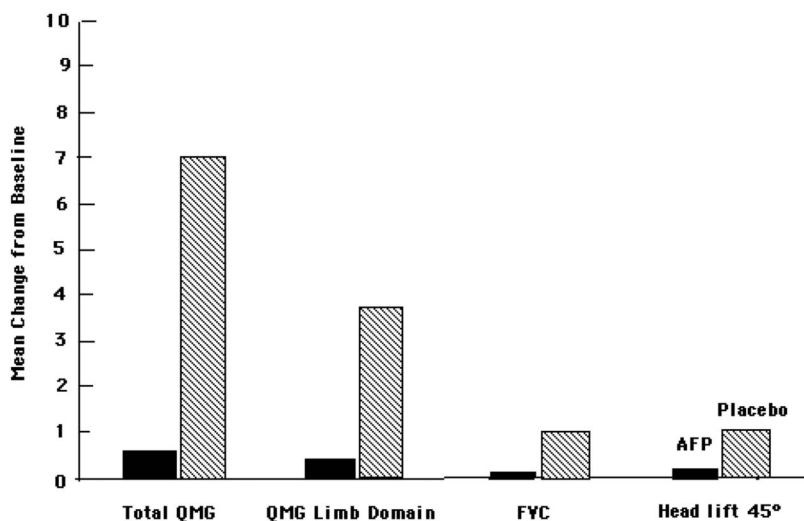DISEASE

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FIGURE 2. Mean CFB after 4 days of amifampridine (AFP; black column) or placebo (hatched column) in total QMG score, QMG-LD score, FVC, and head lift to 45 degrees (head lift 45 degrees).

statistically significant higher proportion of patients had more than a 20% increase in 3TUG average times during treatment with placebo compared with amifampridine phosphate. Furthermore 5 of 13 patients treated with placebo had an increase from baseline in 3TUG of ≥30%. For the QMG-LD score, there was a statistically significant difference in favor of amifampridine phosphate. In patients with LEMS, weakness is usually more pronounced in the proximal muscles, and our data showed that amifampridine phosphate had the greatest effect in proximal muscle function.

The first phase 3 double-blind, randomized study with amifampridine phosphate involved 38 patients in a 14-day trial.[15] Two primary endpoints (QMG and SGI) and one secondary endpoint (CGI-I) were met at day 14, and all 5 endpoints [QMG, SGI, CGI, TFW25 (timed 25-foot walk), and CMAP] were achieved statistical significance at day 8, showing a significant benefit of amifampridine phosphate over placebo. Amifampridine phosphate was well tolerated.

The present 4-day study showed almost the same findings as day 8 in the previous study.[15] In this study, TFW25 was replaced by 3TUG test and CMAP was not tested. Thus, this study confirms again the efficacy and safety of amifampridine phosphate for the symptomatic treatment of LEMS. This study also demonstrated same findings at days 3–8 in the Oh study with 3,4 DAP in QMG and muscle strength scores.[12]

The most striking finding in this study is the difference between mean value at baseline and day 4 in QMG scores: 0.7 for amifampridine phosphate and 7.1 for placebo, indicating that the day 4 difference in QMG score between amifampridine phosphate and placebo is 6.4 in favor of amifampridine phosphate.

The first phase 3 study with amifampridine phosphate showed that the day 8 difference in QMG score between amifampridie phosphate and placebo was 3.9, and the day 14 difference in QMG score was 2.0 for the entire group analysis and 3.0 for the protocol analysis, in favor of amifampridine phosphate.[15] This small difference of QMG score between amifampridine phosphate and placebo at day 14 raised some concern as to whether the QMG test is appropriate for evaluation of muscle function in LEMS.[20,23,24] The previous studies with 3,4 DAP base in LEMS showed 2.25 difference in the day 6 QMG score between 3,4 DAP and placebo in the Sanders study[10] and 2.76 difference in the day 3–8 QMG score in Oh study.[12] According to Barohn et al,[25] the QMG score change should be >2.6 to be

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"of clinical significance" based on 5 MG patients and 4 controls. If Barohn's criterion is applied, "clinically significant improvement" was not achieved in the Sanders study[10] and in the day 14 analysis for the entire group in the first phase 3 study in amifampridine phosphate.[15] Thus, Sanders' concern was understandable. This was due to ocular, bulbar, and distal limb items in the QMG score that are much more common in MG than in LEMS.

However, Oh study of 3,4 DAP base and the previous phase 3 study of amifampridine phosphate demonstrated that QMG score can be used in evaluation of muscle function improvement in LEMS as long as the protocol was followed.[12,15] This study clearly confirmed our view that QMG score is an effective way to evaluate clinical improvement in muscle function in LEMS. Furthermore, muscle function can also be evaluated as muscle strength sum in Oh study[12] and QMG-LD score in this study. It is interesting that FVC score also showed an improvement with amifampridine phosphate. This is not expected in view of rare occurrence of breathing difficulty in LEMS.[26] This most likely represents an improvement in chest muscle function with amifampridine phosphate.

Amifampridine phosphate was well tolerated in this study. During the 4-day study, the most common AEs in the placebo group were muscular weakness and fatigue, followed by dry mouth, asthenia, feeling hot, limb discomfort, muscle spasm, and balance disorder. These are expected from withdrawal of amifampridine phosphate in a patient with LEMS because these are symptoms of untreated disease. In the active group, no major side effect was noted. This confirms the acceptable tolerability of amifampridine phosphate as seen in the first phase 3 study.[15]

Overall, this randomized, double-blind, placebo withdrawal–controlled study demonstrated the benefit of amifampridine phosphate for symptomatic treatment in LEMS.

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