MuSK MG Patients Showed a Positive Response to Amifampridine Phosphate in a Randomized, Placebo-Controlled, Crossover Study

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Background

Anti-MuSK antibodies positive MG is a subclass of the disease characterized by a predominance in females, earlier onset, prominent bulbar involvement, more severe clinical condition, and significant resistance to treatment[1-3]. In these patients, the search for alternative treatment strategies targeting different pathophysiologic aspects of the disease is a medical need.

Amifampridine (3,4-DAP) is a non-specific voltage-dependent potassium (K+) channel blocker already known for its efficacy and safety in the treatment of patients with Lambert-Eaton myasthenic syndrome (LEMS)[4], congenital myasthenic syndromes (CMS)[5] and downbeat nystagmus[6].

Remarkably, it has been described that 3,4 DAP improves neuromuscular transmission in MuSK-MG mice, by predominantly increasing ACh release in the neuromuscular junction[7]. Nonetheless, a MuSK MG patient has been recently successfully treated with 3,4-DAP[8].

Aim

To evaluate safety and efficacy of Amifampridine Phosphate in MuSK MG in a Phase 2b study (MuSK-001)

Methods

PRIMARY OBJECTIVE:

•To characterize the overall safety and tolerability of amifampridine compared with placebo in patients with MuSK-MG.

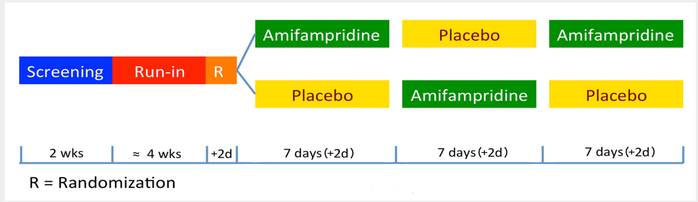
SECONDARY OBJECTIVES:

•To assess the clinical efficacy of amifampridine compared with placebo in patients with MuSK-MG based on improvement in the Myasthenia Gravis-Specific Activities of Daily Living (MG-ADL) scale and in the Quantitative Myasthenia Gravis (QMG) score.

•To assess the clinical efficacy of amifampridine compared with placebo by:

- Myasthenia Gravis Composite (MGC) score;
- Neurological Institute Carlo Besta-Myasthenia Gravis (NICB-MG) scale;
- Fatigue measured by Fatigue Severity Scale (FSS);
- Myasthenia Gravis-Quality of Life (MG-QoL) scale.

STUDY DESIGN:



INCLUSION CRITERIA:

• ≥18 years of age with positive serologic test for anti-MuSK antibodies, MGFA Class II to IV and MGC score equal or greater than 9 points at Screening.

•At Screening, no modifications of: steroids regimen during the month before, PE and IVIG in the previous 3 weeks, immunosuppressants in the last 3 months, rituximab within 6 months before.

EXCLUSION CRITERIA:

•Patients with congenital QT syndromes or concomitant use of drugs potentially causing QTc prolongation, epilepsy, uncontrolled asthma.

•History of thymectomy within 12 months before Screening.

•Concomitant use with sultopride

INVESTIGATIONAL AND REFERENCE PRODUCT:

Amifampridine phosphate 10 mg per tablet and placebo prepared as indistinguishable tablets were provided by Catalyst Pharmaceuticals, Inc.

STATISTIC ANALYSES

A switchback model for three-period, two-treatment crossover design was applied to analyze the change from Baseline (CFB) in all the clinical assessments between Amifampridine phosphate and placebo. The 95% confidence interval (CI) based on this model is presented to show the difference in the Least Squares (LS) means adjusted for carryover effects for each of these analyses. The analyses were performed using SAS PROC MIXED to incorporate the random effects model. All analyses were performed for the Safety Population (SAF) which included all randomized patients who have received at least one dose of study medication and underwent randomization. P value <0.05 was considered statistically significant.

Results

1. Study population. Demographical data for randomized patients are listed below (Table1). Continuous variables are presented as mean, Standard Deviation (SD), Median and minimum and maximum; categorical variables are shown as absolute and relative frequencies. PAP: patients treated with Placebo-Amifampridine-Placebo; APA: patients treated with Amifampridine-Placebo-Amifampridine.

TABLE 1

			PAP(n=4)	APA(n=3)	Total(n=7)
Age, years		Mean (SD)	46.3 (7.9)	39.7 (4.0)	43.4 (7.0)
		Median (Min,Max)	43.0 (41.0,58.0)	42.0 (35.0,42.0)	42.0 (35.0,58.0)
Sex	Male	n(%)	0(0.0%)	1(33.3%)	1(14.3%)
	Female	n(%)	4(100.0%)	2(66.7%)	6(85.7%)
Age at onset, years		Mean (SD)	40.0 (8.8)	33.0 (14.7)	37.0 (11.2)
		Median (Min,Max)	36.5 (34.0,53.0)	41.0 (16.0,42.0)	37.0 (16.0,53.0)
Previous treatment	No	n(%)	1(25.0%)	0(0.0%)	1(14.3%)
	Yes	n(%)	3(75.0%)	3(100.0%)	6(85.7%)

2. Primary outcome results: 3,4 DAP treatment is safe in MuSK-MG patients. Number of patients presenting an adverse event (AE) (Table 2) and kind of treatment AE (Table 3) are shown. TEAE = any AE started at or after the date of randomization. Percentages are based on the Number of subjects in the population. n = number of patients; E = number of events. No related TEAEs were reported in the study.

TABLE 2

	Amifampridine (N=7)		Placebo (N=7)	
	n (%)	E	n (%)	E
No. of patients with at least one TEAE	1 (14.3%)	2	1 (14.3%)	1
No. of patients with at least one TESAE	0	0	0	0
No. of patients with at least one TEAE leading to discontinuation	0	0	0	0
No. of patients with at least one TEAE leading to death	0	0	0	0

TABLE 3

	Amifampridine (N=7)		Placebo (N=7)	
	n (%)	E	n (%)	E
Eye disorders: chalazion	1 (14.3%)	1		
Infections and infestations: cystitis			1 (14.3%)	1
Injury, poisoning and procedural complications: corneal abrasion	1 (14.3%)	1		

3. Secondary outcome results: 3,4 DAP treatment is effective in MuSK-MG patients. Results from a switchback model for three-period, two-treatment crossover design applied on change from Baseline (CFB) of all scales are reported (Table 4). The Least Square (LS) Means, p-values, and 95% CI were obtained using a 3-period 2-treatment crossover model through Day 21. SE standard error. CFB=Change from Baseline (Day 0); P<0,05 is statistically significant.

TABLE 4

	LS Mean (SE)		LS Mean Difference (95% CI)	
	Amifampridine (n=10)	Placebo (n=11)		P-value
MG-Specific Activities of Daily Living	-0.111 (1.074)	5.611 (1.007)	-5.72 (-8.33, -3.12)	0.0006
Quantitative MG	0.056 (1.098)	6.917 (1.034)	-6.86 (-9.75, -3.98)	0.0003
MG Composite	0.139 (1.643)	11.611 (1.535)	-11.5 (-15.2, -7.70)	<0.0001
Neurological Institute Carlo Besta MG	-5364 (45414)	180166 (42216)	19E4 (-28E4, -91E3)	0.0014
MG-Quality of Life	-2.111 (5.192)	16.389 (4.816)	-18.5 (-28.8, -8.21)	0.0025
Fatigue Severity Scale	-10.00 (4.387)	7.583 (4.126)	-17.6 (-28.9, -6.27)	0.0061

Conclusions

•The present study indicates that Amifampridine has a good safety profile in MuSK MG patients, achieved via preemptive cardiac screening and careful monitoring.

•Amifampridine showed a measurable evidence of benefit in all the outcome measures in study (MGC, QMG, NICB, MG-ADL, MG-QoL and FSS scores) resulting in an effective symptomatic treatment for MuSK-MG.

•A multicentric, randomized, controlled trial is needed to validate the clinical efficacy of Amifampridine in Musk MG-affected patients.

References

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