Long-Term Efficacy of Dichlorphenamide for the Treatment of Primary Periodic Paralysis

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Introduction

- Primary periodic paralyses (PPP) are rare, hereditary skeletal muscle channelopathies (ie, hyperkalemic PPP [HYP], hypokalemic PPP [HOP]) characterized by muscle weakness[1]
- Treatment with dichlorphenamide (DCP) for 9 weeks has been shown to be efficacious for reducing weekly attack rates in patients with PPP[2,3]

Aim

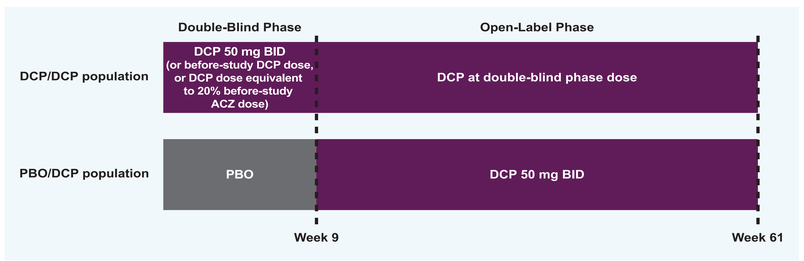
- To evaluate the long-term (up to 61 weeks) efficacy of DCP treatment for PPP

Methods

Study Design and Patients

- Adults in the randomized, double-blind, placebo (PBO)-controlled HYP/HOP trial were randomly assigned to receive DCP (current DCP dose if taking DCP before study start or DCP 50 mg twice daily; patients receiving acetazolamide before study start were assigned a DCP dose equivalent to 20% of the acetazolamide dose) or PBO for 9 weeks during a double-blind phase, followed by a 52-week open-label phase (**Figure 1**)[2]
  - Patients in the open-label DCP group continued at the same dose they were taking at the end of the 9-week double-blind phase (with dose adjustments permitted; DCP/DCP population)
  - Patients in the PBO group switched to DCP 50 mg twice daily in the open-label phase (PBO/DCP population)

Figure 1. Study Design



ACZ = acetazolamide; BID = twice daily; DCP = dichlorphenamide; PBO = placebo.

Assessments and Statistical Analyses

- The study completer population included patients in the intent-to-treat (ITT; all patients randomly assigned in the double-blind phase to DCP or PBO) population who completed the open-label phase of the study
- Changes from baseline to Weeks 9 and 61 and from Weeks 9 to 61 in attack rates and severity-weighted attack rates were analyzed for within- and between-group median differences
- The median difference between time points in weekly attack rates and severity-weighted attack rates within a treatment group was assessed for statistical significance using Wilcoxon signed-rank test
- Between-treatment comparisons of the changes from baseline to Weeks 9 and 61 and from Weeks 9 to 61 were made using blocked Wilcoxon rank sum test, adjusting for type of PPP

Results

Demographic and Baseline Characteristics

- 63 patients were included in the ITT analyses: 36 were in the DCP/DCP group and 27 in the PBO/DCP group (**Table 1**)
  - 47 patients (74.6%) completed 61 weeks of treatment (study completer population)

Table 1. Demographic and Baseline Disease Characteristics

	ITT Population		Study Completer Population	
Parameter	**DCP/DCP (n=36)**	**PBO/DCP (n=27)**	**DCP/DCP (n=26)**	**PBO/DCP (n=21)**
Age, y				
Mean (SD)	42.9 (13.3)	45.2 (15.6)	40.9 (14.2)	43.4 (15.9)
Range	19–76	19–76	19–76	19–76
Male, n (%)	22 (61.1)	17 (63.0)	17 (65.4)	13 (61.9)
Race, n (%)				
White	30 (83.3)	23 (85.2)	22 (84.6)	17 (81.0)
Hispanic	4 (11.1)	2 (7.4)	3 (11.5)	2 (9.5)
Other	2 (5.6)	1 (3.7)	1 (3.8)	1 (4.8)
Not reported	0	1 (3.7)	0	1 (4.8)
Type of periodic paralysis, n (%)				
Hyperkalemic	12 (33.3)	8 (29.6)	9 (34.6)	7 (33.3)
Hypokalemic	24 (66.7)	19 (70.4)	17 (65.4)	14 (66.7)
Median weekly attack rate	1.75	2.25	1.75	3.00

DCP = dichlorphenamide; ITT = intent-to-treat; PBO = placebo; SD = standard deviation.

Efficacy

- For patients in the study completer population, the median weekly attack rate and median severity-weighted attack rate improved significantly from baseline to Week 61 in both treatment groups (**Table 2; Figure 2; Figure 3**)

Table 2. Summary of Efficacy From Baseline to Week 61

	ITT Population		Study Completer Population	
Outcome	**DCP/DCP (n=36)**	**PBO/DCP (n=27)**	**DCP/DCP (n=26)**	**PBO/DCP (n=21)**
Median weekly attack rate				
Baseline	1.75*	2.25†	1.75‡	3.00§
Week 61			0.06	0.25
Median decrease from baseline to Week 61			1.00	0.63
Median % decrease from baseline to Week 61			93.8	75.0
P value¶			<0.0001	0.01
Median severity-weighted attack rate				
Baseline	3.25*	5.88†	2.25‡	5.88§
Week 61			0.06	0.50
Median decrease from baseline to Week 61			2.25	1.69
Median % decrease from baseline to Week 61			97.1	80.8
P value¶			<0.0001	0.01

*n=35. †n=26. ‡n=25. §n=20. ¶Based on median decrease from baseline to Week 61 within a group.
DCP = dichlorphenamide; ITT = intent-to-treat; PBO = placebo.

- For patients in the study completer population, the median weekly attack rate and median severity-weighted attack rate decreased from Week 9 (start of open-label DCP treatment) to Week 61 for patients in both the DCP/DCP and PBO/DCP groups; in the PBO/DCP group, the median decrease from Week 9 to Week 61 in the weekly attack rate was significant (*P*=0.049; **Table 3**)

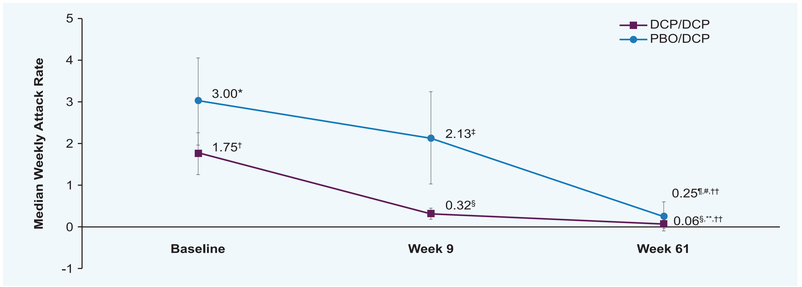
Table 3. Summary of Efficacy From Week 9 to Week 61

	ITT Population		Study Completer Population	
Outcome	**DCP/DCP (n=36)**	**PBO/DCP (n=27)**	**DCP/DCP (n=26)**	**PBO/DCP (n=21)**
Median weekly attack rate				
Week 9*	0.49†	1.78‡	0.32	2.13§
Week 61¶			0.06	0.25
Median decrease from Week 9 to Week 61			0.14	1.04
Median % decrease from Week 9 to Week 61			77.1	62.7
P value#			0.1	0.049
Median severity-weighted attack rate				
Week 9*	0.63†	4.34‡	0.58	5.02§
Week 61**			0.06	0.50
Median decrease from Week 9 to Week 61			0.24	2.72
Median % decrease from Week 9 to Week 61			72.6	57.8
P value#			0.09	0.08

*Start of open-label DCP treatment. †n=35. ‡n=20. §n=16. ¶The between-group difference for the change from Week 9 to Week 61 was significant (*P*=0.04). #Based on median decrease from Week 9 to Week 61 within a group. **The between-group difference for the change from Week 9 to Week 61 was significant (*P*=0.047).
DCP = dichlorphenamide; ITT = intent-to-treat; PBO = placebo.

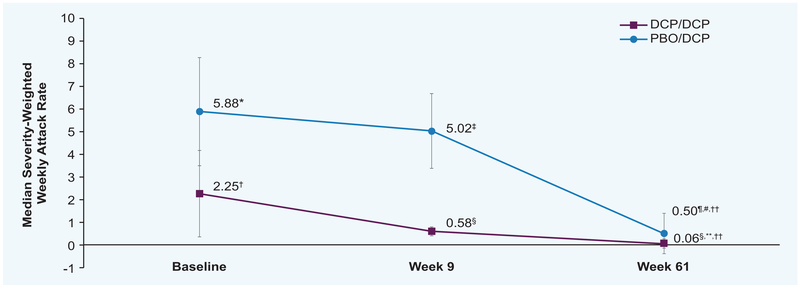
- Between-group differences in median weekly attack rates (**Figure 2**) and median severity-weighted weekly attack rates (**Figure 3**) were not significant for changes from baseline at Week 61

Figure 2. Median Weekly Attack Rates at Baseline, Week 9, and Week 61 (Study Completer Population)



Bars represent standard error. Attack rates at Week 9 and Week 61 are the mean of the weekly attack rates at Weeks 2–9 and Weeks 54–61. For patients with <8 weeks of completed diary entries, missing data were considered as days without an attack in a particular week.
*n=20. †n=25. ‡n= 16. §n=26. ¶n= 21. #*P*=0.01. **P<0.0001. ††*P* value based on median decrease from baseline to Week 61 within a group.
DCP = dichlorphenamide; PBO = placebo.

Figure 3. Median Severity-Weighted Weekly Attack Rates at Baseline, Week 9, and Week 61 (Study Completer Population)



Bars represent standard error. Severity-weighted attack rates at Week 9 and Week 61 are the mean of the weekly severity-weighted attack rates at Weeks 2–9 and Weeks 54–61. For patients with <8 weeks of completed diary entries, missing data were considered as days without an attack in a particular week.
*n=20. †n=25. ‡n=16. §n=26. ¶n= 21. #*P*=0.01. **P<0.0001. ††*P* value based on median decrease from baseline to Week 61 within a group.
DCP = dichlorphenamide; PBO = placebo.

Conclusion

- **Long-term (52 or 61 weeks) DCP treatment was efficacious and provided durable reduction in attack frequency and severity in patients with PPP**

References

1. Statland JM, et al. *Muscle Nerve*. 2018;57(4):522-530. 2. Sansone VA, et al. *Neurology*. 2016;86(15):1408-1416. 3. Tawil R, et al. *Ann Neurol*. 2000;47(1):46-53.

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