Characterization of Common Adverse Events in a Phase 3, Placebo-Controlled, Double-Blind and Open-Label Extension Study of Dichlorphenamide for Primary Periodic Paralysis

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Introduction

- Primary periodic paralysis (PPP) is a rare condition caused by genetic mutations in skeletal muscle sodium, calcium, and potassium channels, resulting in attacks of muscle weakness[1,2]
- Dichlorphenamide (DCP), administered daily for up to 1 year, has been shown to reduce the frequency, severity, and duration of attacks of PPP[3,4] and was approved in the United States for the treatment of primary hyperkalemic and hypokalemic periodic paralysis and related variants in 2015[5]
- The most common adverse events (AEs) observed during clinical trials were paresthesia and cognition-related AEs[3,4]
  - In the double-blind phase of the HYP/HOP trial (n=65), compared with placebo, DCP-treated patients had higher rates of paresthesia (placebo, 14% vs DCP, 47%) and cognitive disorder (placebo, 7% vs DCP, 19%)[3]
- To further consider the safety profile of DCP, additional characterization of these AEs was conducted

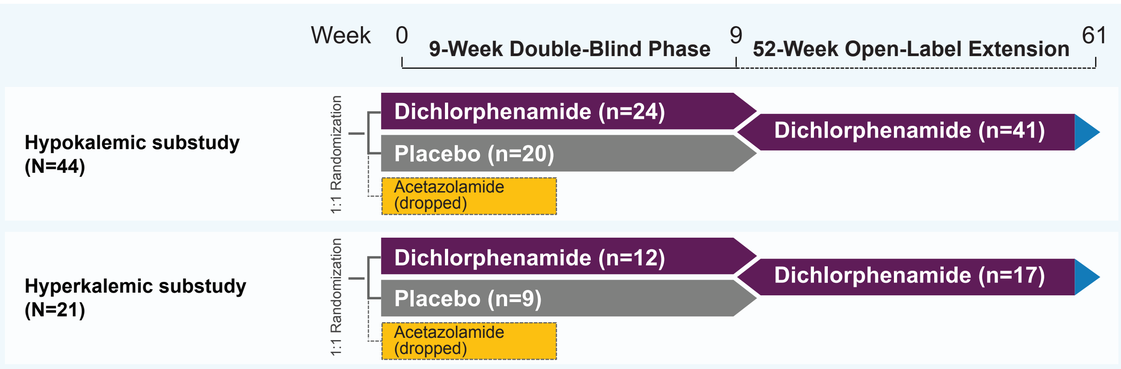
Objective

- To further characterize the time course, intensity, and outcomes of paresthesia and cognition-related AEs during 61 weeks of DCP treatment for PPP

Methods

- Data were analyzed from a 9-week phase 3, randomized, double-blind, placebo-controlled phase and a 52-week open-label extension phase (**Figure 1**)[3]
  - The trial included 2 substudies (1 in adults with hyperkalemic periodic paralysis and 1 in adults with hypokalemic periodic paralysis); data were pooled
    - Patients were randomly assigned to receive DCP (current DCP dose if taking before study start or 50 mg twice daily), placebo (PBO), or acetazolamide (this arm was later dropped due to low enrollment [n=5] and was not included in these analyses) during the double-blind phase, with dose reductions allowed because of intolerable AEs; during the open-label phase, patients received DCP 50 mg twice daily or continued at the same dose they were taking at the end of the 9-week double-blind phase, with dose adjustments permitted
    - AEs reported during DCP exposure were summarized by double-blind treatment/open-label treatment (PBO/DCP or DCP/DCP) group

Figure 1. Study Design



Data from Sansone VA, Burge J, McDermott MP, et al. *Neurology.* 2016;86(15):1408-1416.[3]

- Medical Dictionary for Regulatory Activities high-level group terms of deliria (including confusion) and mental impairment disorders were pooled for cognition-related events
- Kaplan-Meier methods were used to estimate the percentages of patients with no occurrence of the AEs over time

Results

- Two of 65 patients who received double-blind treatment with PBO discontinued from the study before the extension phase; therefore, 63 patients were included in the analysis (PBO/DCP, n=27; DCP/DCP, n=36) of paresthesia and cognition-related AEs during DCP exposure
  - Majority of the 63 patients were male (61.9%), white (84.1%), and had hypokalemic periodic paralysis (68.3%); the age range was 19 to 76 years

Paresthesia Adverse Events

- Overall, 25 of 63 (39.7%) patients treated with DCP had ≥1 AE of paresthesia during the 61-week study duration (**Table 1**)
  - No AEs of paresthesia were considered severe in intensity and only 1 of the 63 patients discontinued from the study due to paresthesia
  - 6 of 25 (24.0%) patients with paresthesia had a reduction in the dose of DCP and the paresthesia AE was resolved in 5 of the 6 cases

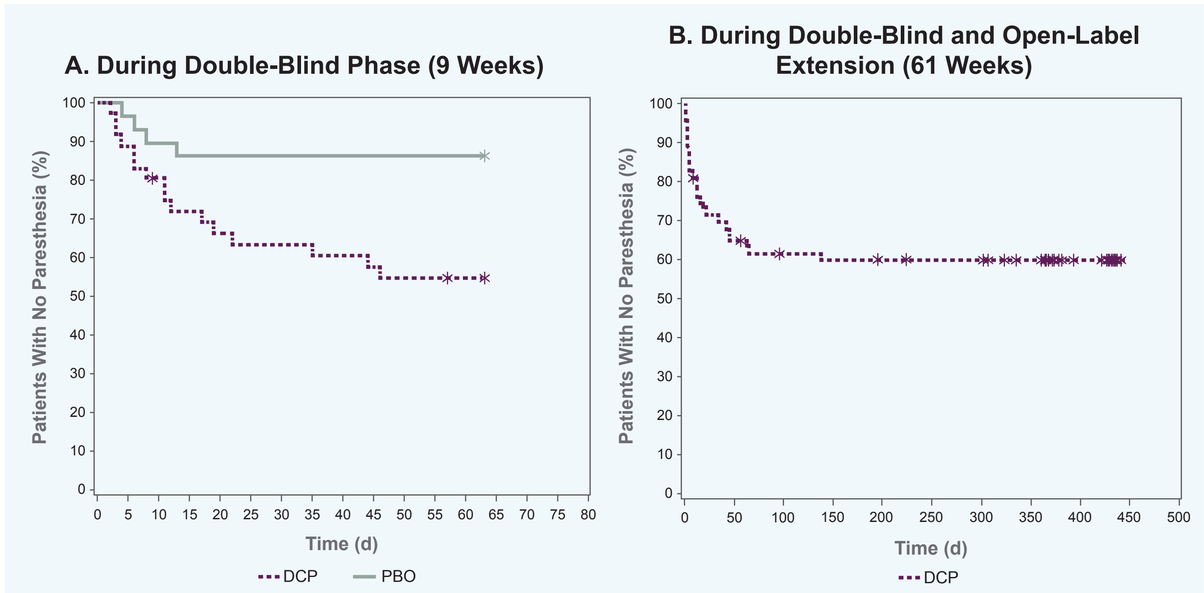
Table 1. Characterization of Adverse Events of Paresthesia During DCP Treatment

Paresthesia	Patients, n (%) (n=63)
Any paresthesia AE	25 (39.7)
Any drug-related paresthesia AE*	24 (38.1)
Discontinuation due to paresthesia AE	1 (1.6)
AE intensity	
Mild	11 (17.5)
Moderate	14 (22.2)
Severe	0 (0.0)
Resolution of last paresthesia AE	
Resolved	19 (30.2)
Under treatment/observation	6 (9.5)

*Considered by investigators to be at least possibly related to study drug.
AE = adverse event; DCP = dichlorphenamide; SD = standard deviation.

- Onset of paresthesia typically occurred during the first 4 weeks of DCP treatment (**Figures 2A and 2B**)

Figure 2. Time to Onset of Paresthesia



Symbol "*" denotes censored data.
DCP = dichlorphenamide; PBO = placebo.

Cognition-Related Adverse Events

- Overall, 16 of 63 (25.4%) patients treated with DCP had ≥1 cognition-related AE during the 61-week study duration (**Table 2**)
  - The majority of cognition-related AEs were mild in intensity, and 4 of the 63 patients (6.3%) discontinued from the study due to a cognition-related AE
  - 6 of 16 (37.5%) patients with cognition-related AEs had a reduction in the dose of DCP and the cognition-related AE was resolved in all 6 cases

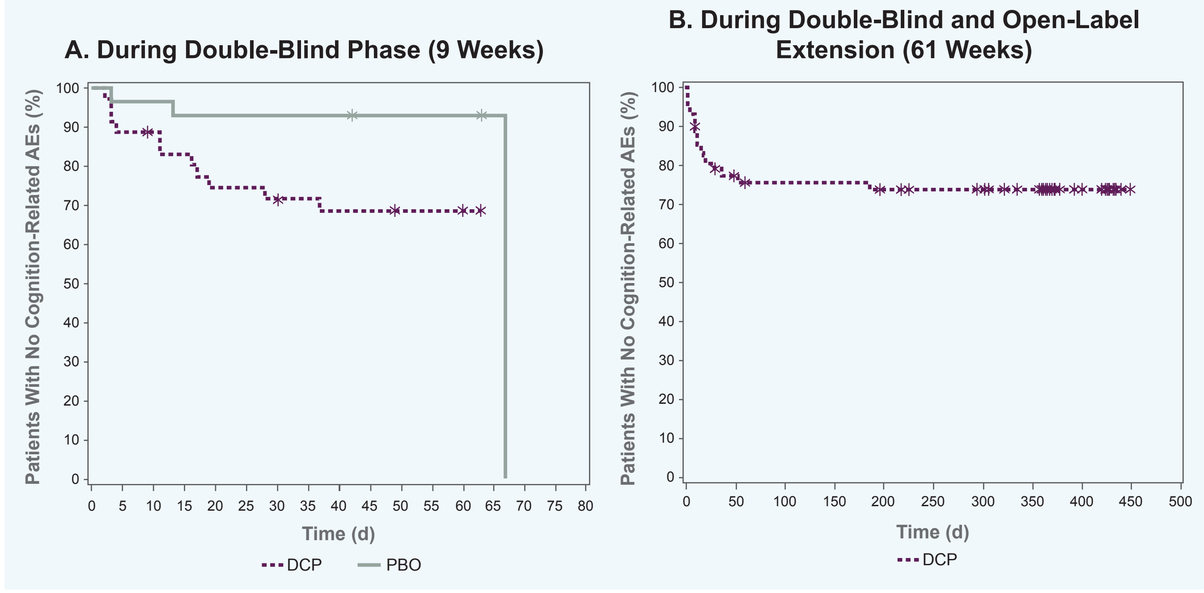
Table 2. Characterization of Cognition-Related Adverse Events During DCP Treatment

Cognition-Related AEs	Patients, n (%) (n=63)
Any cognition-related AE	16 (25.4)
Any drug-related cognition-related AE*	16 (25.4)
Discontinuation due to cognition-related AE	4 (6.3)
AE intensity	
Mild	9 (14.3)
Moderate	5 (7.9)
Severe	2 (3.2)
Resolution of last cognition-related AE	
Resolved	11 (17.5)
Under treatment/observation	5 (7.9)

*Considered by investigators to be at least possibly related to study drug.
AE = adverse event; DCP = dichlorphenamide; SD = standard deviation.

- Onset of cognition-related AEs typically occurred during the first 4 weeks of DCP treatment (**Figures 3A and 3B**)

Figure 3. Time to Onset of Cognition-Related Adverse Events



Symbol "*" denotes censored data.
AE = adverse event; DCP = dichlorphenamide; PBO = placebo.

Conclusions

- **Paresthesia and cognition-related AEs tended to be mild or moderate in intensity and nearly always first occurred early (eg, within 1 month) after therapy initiation**
- **These AEs uncommonly resulted in discontinuation from the study and were sometimes managed by DCP dose reductions**
- **Reduction in dose was frequently associated with resolution of these events, suggesting a potential intervention to hasten resolution**

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