SUPPLEMENTARY MATERIAL

Supplementary e-Table 1: Diagnostic criteria

Causes of secondary HYP or HOP were excluded (deranged serum potassium, thyroid disease, adrenal disease, laxative abuse, diuretics), and long QT on ECG was ruled out. Participants were then classified as follows:

Genetically definite: Criteria 1 & 2 from the list below
Clinically definite: Criteria 2 &5 plus either Criterion 3 or Criterion 4
Clinically probable: Criteria 2 & 5 only
Not HYP or HOP

Criteria

1) Mutation in SCN4A or CACNA1S associated with HYP or HOP
2) Two attacks of tetraparesis or 1 attack with a family history of attacks of HYP or HOP
3) Hyperkalaemia (HYP) / Hypokalaemia (HOP) during a documented attack in the subject or a family member
4) Family history of HYP / HOP
5) Typical clinical features including all (HOP) or at least 3 (HYP) of the following:
   Typical external triggers (HYP: rest, potassium load, fasting / HOP: rest, rest after exercise, carbohydrate load)
   Onset before age 30
   For HOP only - Positive response to oral potassium
   Typical attack duration (HYP < 2 hrs, HOP > 2 hrs)
   Positive long exercise test (>40% decrement in CMAP)

Supplementary e-Table 2: Exclusion criteria

1. Known mutation in the α subunit of sodium channel (HOP trial only).
2. Evidence for Andersen-Tawil syndrome (any one of the following 3 criteria)
   a. Prolonged QT interval or complex ventricular ectopy between attacks
   b. KIR 2.1 gene mutation
   c. Distinctive physical features (2 out of 5)
      - Low set ears
      - Short stature
      - Hypo-/micrognathia
      - Clinodactyly
      - Hypo-/hypertelorism

3. Coincidental renal, hepatic, active thyroid disease, restrictive or obstructive lung disease, or heart disease
4. Chronic, non-congestive, angle-closure glaucoma
5. Use of any of the following medications for reasons other than treatment of periodic paralysis: diuretics, antiarrhythmics, corticosteroids, beta-blockers, calcium channel blockers, antiepileptics, magnesium
6. History of life-threatening episodes of respiratory muscle weakness or cardiac arrhythmias during attacks
7. History of worsening symptoms with the use of carbonic anhydrase inhibitors
8. Any other neuromuscular disease

Supplementary e-Table 3: Adverse events in the 52-week extension phase

ADVERSE EVENT	HOP (N=40)	HYP (N = 17)
Paraesthesia	12 (30.0%)	9 (52.9%)
Neuropsychiatric *	11 (27.5%)	2 (11.8%)
Fall	7 (17.5%)	
Headache	5 (7.5%)	
Fatigue or Lethargy	6 (15.0%)	
Pain in extremity	4 (10.0%)	
Dysgeusia	4 (10.0%)	
Nasopharyngitis	3 (7.5%)	
Muscle spasms	3 (7.5%)	
Nephrolithiasis	3 (7.5%)	
Constipation	2 (5.0%)	
Diarrhoea	2 (5.0%)	
Gastrooesophageal reflux	2 (5.0%)	
Peripheral Oedema	2 (5.0%)	
Muscular weakness	2 (5.0%)	
Rash	2 (5.0%)	

Values presented are the number (%) of subjects who reported at least one occurrence of the event
*Confusion, impaired cognition, or impaired memory

Appendix e-1 SUPPLEMENTARY MATERIALS AND METHODS

The study drug was manufactured such that placebo and dichlorphenamide were matched as closely as possible with respect to appearance and taste.

Details of Randomization

The computer-generated randomization plan was prepared at the Muscle Study Group (MSG) Biostatistics Center and sent to the University of Rochester Clinical Materials Services Unit (Rochester, NY) and Aptuit Operations (Inchwood Bathgate, UK) who labelled and distributed the drug. The order of assignment of the randomization numbers within each stratum was provided to a masked information analyst in the Clinical Trials Coordination Center (CTCC, Rochester, NY) so that this information could be incorporated in the web-based enrollment module. The only individuals with access to the treatment assignments were the programmer who generated the randomization plan, an independent statistician who liaised with the Data and Safety Monitoring Board (DSMB), and staff responsible for labeling study medication. These individuals did not communicate with any other staff involved in the trial about study-related matters.

Sample size calculation

The sample sizes were originally chosen to provide adequate power to detect effects of DCP of the magnitude that were observed in a previously published trial of DCP (1). For the HOP subjects, the mean ± standard deviation of attack rates for participants not reaching the endpoint

of acute worsening was 1.8 ± 2.3 for participants on placebo and 1.0 ± 1.8 for participants on DCP. Also, 15/35 HOP participants (43%) reached the endpoint of acute worsening while on placebo, compared to 5/35 HOP participants (14%) on DCP. For the HYP subjects, the mean ± standard deviation of attack rates was 3.7 ± 3.8 for participants on placebo and 1.8 ± 3.1 for participants on DCP not reaching the endpoint of acute worsening (which occurred in only five cases, 3 on placebo and 2 on DCP).

To compute power for a given sample size, independent bootstrap samples were taken from the observed attack rates in the DCP and placebo conditions (with arbitrary large values assigned to subjects who reached the endpoint of acute worsening) and a Wilcoxon rank sum test was used to compare the two groups. This was repeated 10,000 times and power was estimated as the percentage of times (out of 10,000) that the null hypothesis was rejected (2). In order to detect effects of DCP (vs. placebo) of the magnitudes described above with power > 85%, sample sizes of 48 HOP participants (24 per group) and 64 HYP participants (32 per group) were required. To account for an anticipated 10% attrition rate, the total sample size was inflated by a factor of $1/(1\text{-}0.10)^2 = 1.23$, yielding 60 HOP participants (30 per group) and 80 HYP participants (40 per group). Due to difficulties in recruitment, these sample sizes were not achieved in the trials.

Evaluations at each visit

Subjects had visits at screening (1-2 months prior to baseline), baseline, and Weeks 9, 35, and 61. At screening, a complete medical history was obtained and the diagnosis of either HOP or HYP was verified. Vital signs, ECG, urinalysis, complete blood count, and serum chemistries with standard measures of kidney and liver function were obtained. Strength was assessed clinically (manual muscle testing, MMT) and quantitatively (maximal voluntary isometric

contraction testing, MVICT) (3, 4). A composite MMT score was derived by averaging the MRC scores (0-5 scale) across 26 movements: shoulder abductor (left/right), elbow extensor (left/right), elbow flexor (left/right), wrist extensor (left/right), wrist flexor (left/right), hip flexor (left/right), hip extensor (left/right), hip abductor (left/right), knee extensor (left/right), knee flexor (left/right), ankle dorsiflexor (left/right), ankle plantar flexor (left/right), neck extensor, and neck flexor. MVICT was measured for elbow extension (left/right), elbow flexion (left/right), knee extension (left/right), knee flexion (left/right), and hand grip (left/right). Composite MVICT scores were formed as an average standardized MVICT score (average Z-score) and an average percent of predicted normal score using a normative database (3). Health-related quality of life was assessed using the SF-36v2 (5, 6). Subjects also completed the Symbol Digit Modalities test (7), Profile of Mood States (POMS) (8), and Trail Making Test Parts A and B (9). Subjects maintained a daily attack diary by telephone using an interactive voice response (IVR) system (10) to document the maximum severity and duration of every paralytic attack. Each distinct attack was recorded on a separate call and the date and time of day specified at each phone call. Severity was graded on a 1-10 scale (1 = not at all severe, 5 = moderate, 10 = extremely severe). Telephone calls were to be made daily for the entire 9-week double-blind phase. For the Italian site, English-Italian translations and then back translations (Italian-English) were verified by an official translator.

At the baseline visit, the physical examination, vital signs, and strength testing were repeated. Lean body mass was measured using dual X-ray absorptiometry (DEXA) (11). An ultrasound (kidneys, ureter, and bladder) was performed to screen for nephrolithiasis. Completion of the telephone diary was reviewed and adverse events and concomitant medications were recorded. Subjects were randomized to receive either DCP or placebo, started taking study medication, and

were monitored during a 3-day inpatient visit.

At Weeks 9 and 61, subjects had a physical examination, laboratory tests were performed, and lean body mass was evaluated. At Weeks 9, 35, and 61, vital signs, strength testing, and neuropsychological testing were performed and quality of life forms were completed. Reviews of telephone diary completion, adverse events, concomitant medications, and compliance with study medication (pill counts) were also performed. An ultrasound was repeated at Week 61. Subjects and site investigators were asked to guess the subject's assigned treatment at Week 9. The site coordinator made weekly phone calls to each subject to monitor telephone diary completion (when applicable) and adverse events.

Appendix e-2 BASELINE CHARACTERISTICS

HOP Participants

The baseline characteristics were comparable between the HOP subjects assigned to DCP (n = 24) and those assigned to placebo (n = 20) (Table 1). Fifty-five percent of subjects were enrolled in US centers and 45% in the UK and Italy. The mean age across all HOP subjects was 44.5 ± 14.9 years, most subjects (73%) were male, and only 28% were treatment-naive. Genetic information was available in 38 of 44 subjects in the HOP trial. Information was not available in 6 and no mutation was identified in 5 subjects. Sequencing the CACNA1S gene disclosed the R528H mutation in 19 subjects, R1239H in 10 subjects, and R489H in 1 subject. The remaining 3 subjects had hypokalemic periodic paralysis type 2, with mutations in SCN4A (I1495T, R675G, and R222W).

HYP Participants

The baseline characteristics were comparable between the HYP subjects assigned to DCP (n = 12) and those assigned to placebo (n = 9) (Table 1). Sixty-two percent of subjects were enrolled in US centers and 38% in the UK and Italy. The mean age was 42.6 ± 13.7 years, most subjects (57%) were female, and 52% were treatment-naive. Genetic information was available in 16 of 21 subjects in the HYP trial. The identified mutations included T704M (n = 8), R1448C (n = 1), R1448G (n = 1), R675Q (n = 1), and M1592V (n = 2). Sequencing of regions of SCN4A where mutations are commonly found was negative in 3 subjects.

Appendix e-3 COMPLIANCE, DOSAGE OF DCP AND BLINDING

HOP Trial

Median (IQR) compliance with diary reporting via the IVR system (percentage of days with a report out of those expected) was 62% (43%, 79%) in the DCP group and 55% (18%, 88%) in the placebo group.

In the double-blind phase, the average overall compliance with study medication was 92% ± 14% in the DCP group and 91% ± 14% in the placebo group.

DOSAGE OF DCP

In the HOP subjects, for the 9-week double blind phase, the mean dosage of DCP was 93.75mg/day with an overall compliance of 92.41 %. The mean dosage of placebo was 107.50 mg/day with an overall compliance of 90.83 %.

BLINDING

At the end of the double-blind phase, investigators guessed that 20/22 (91%) subjects in the DCP group and 3/17 (18%) subjects in the placebo group were on DCP ($p < 0.0001$). For those correctly identified to be in the DCP group, the guess was based on improvement in symptoms (65%), adverse events (25%), and other (10%). For those correctly identified in the placebo group, the primary reason for the guess was lack of improvement in symptoms in 86%.

HYP Trial

Median (IQR) compliance with diary reporting via the IVR system (percentage of days with a report out of those expected) was 28% (18%, 50%) in the DCP group and 55% (2%, 75%) in the placebo group.

In the 9-week double-blind phase, the average overall compliance with study medication was 91% ± 13% in the DCP group and 95% ± 5% in the placebo group.

DOSAGE OF DCP

The mean dosage of DCP at Week 9 was 77.1 ± 31.0 mg/day in the DCP group and 83.3 ± 25.0 mg/day in the placebo group.

BLINDING

At the end of the double-blind phase, investigators guessed that 9/10 (90%) subjects in the DCP group and 1/8 (13%) subjects in the placebo group were on DCP ($p = 0.003$). For those correctly identified to be in the DCP group, the primary reasons for the guess included improvement in

symptoms (30%), lack of improvement in symptoms (10%), and adverse events (50%). For those correctly identified in the placebo group, the primary reason for the guess was lack of improvement in symptoms in 71%.

Appendix e-4 References

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