RESEARCH ARTICLE

Triheptanoin Did Not Show Benefit versus Placebo for the Treatment of Paroxysmal Movement Disorders in Glut1 Deficiency Syndrome: Results of a Randomized Phase 3 Study

Valentina De Giorgis, MD, PhD,[1*] Kailash P. Bhatia, FRCP,[2] Odile Boespflug-Tanguy, MD,[3] Domitille Gras, MD,[3] Adela Della Marina, MD,[4] Archana Desurkar, MD,[5] Manuel Toledo, MD,[6] Ian Miller, MD,[7] Michael Rotstein, MD,[8] Susanne A. Schneider, MD,[9] Daniel C. Tarquinio, DO,[10] Yvonne Weber, MD,[11,12] Melanie Brandabur, MD,[13] Jill Mayhew, PT,[13] Tony Koutsoukos, PhD,[13] and Darryl C. De Vivo, MD[14]

[1]*Department of Child Neurology and Psychiatry, Mondino Foundation, Pavia, Italy*
[2]*Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, National Hospital for Neurology and Neurosurgery, Queen Square, London, United Kingdom*
[3]*Service de Neurologie Pédiatrique, Centre de Référence Leucodystrophies et Leucoencephalopathies de Cause Rare (LEUKOFRANCE), APHP Robert-Debré, Paris, France*
[4]*Department of Pediatric Neurology, Centre for Neuromuscular Disorders, Centre for Translational Neuro- and Behavioral Sciences, University Hospital Essen, University Duisburg-Essen, Essen, Germany*
[5]*Neurology Department, Sheffield Children's National Health Service Foundation Trust, Sheffield, United Kingdom*
[6]*Epilepsy Unit, Neurology Department, Hospital Vall d'Hebron, Barcelona, Spain*
[7]*Department of Neurology and Comprehensive Epilepsy Program, Brain Institute, Miami Children's Hospital, Miami, Florida, USA*
[8]*Pediatric Movement Disorders Service, The Pediatric Neurology Unite and Child Development Center, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel*
[9]*Department of Neurology, Ludwig-Maximilians-University of München, Munich, Germany*
[10]*Center for Rare Neurological Diseases, Norcross, Georgia, USA*
[11]*Department of Neurology and Epileptology, Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany*
[12]*Section of Epileptology, Department of Neurology, University Hospital RWTH Aachen, Aachen, Germany*
[13]*Ultragenyx Pharmaceutical Inc., Novato, California, USA*
[14]*Department of Neurology and Pediatrics, Columbia University, New York, New York, USA*

ABSTRACT: Background: Paroxysmal movement disorders are common in Glut1 deficiency syndrome (Glut1DS). Not all patients respond to or tolerate ketogenic diets.

Objectives: The objective was to evaluate the effectiveness and safety of triheptanoin in reducing the frequency of disabling movement disorders in patients with Glut1DS not receiving a ketogenic diet.

***Correspondence to:** Dr. V. De Giorgis, Department of Child Neurology and Psychiatry, Mondino Foundation, Via Mondino 2, 27100 Pavia, Italy; E-mail: valentina.degiorgis@mondino.it

Relevant conflicts of interest/financial disclosures: V.D.G. has received speaker fees from GW Pharmaceuticals, Eisai, and Neuraxpharm and consultant fees from Nutricia, Kanso Dr. Schär, and Vitaflo. A.D.M. has received speaker fees and honoraria from Nutricia. M.T. has received speaker fees and honoraria from GW Pharmaceuticals, Eisai, UCB Pharma, BIAL, Angelini, BIAL, and Neuraxpharm. S.A.S. has participated in Else Kröner-Fresenius-Stiftung, LMU Clinician Scientist Programme and has received lecturing fees from Nutricia. Y.W. has received speaker fees and honoraria from Eisai, Arvelle Therapeutics, UCB Pharma, Jazz Pharmaceuticals, Dr. Schär, and Zogenix. M.B., J.M., and T.K. are employees of and have stock ownership in Ultragenyx Pharmaceutical Inc. D.C.D. is an advisor/consultant for AveXis, Biogen, Cytokinetics, Ionis Pharmaceuticals, Metafora Biosystems, Roche, Sanofi, Sarepta, and SMA Foundation; has received research grants from Hope for Children Research Foundation, National Institutes of Health, SMA Foundation, Cure SMA, Glut1 Deficiency Foundation, and United States Department of Defense; has received clinical trial funding from Biogen, Mallinckrodt, PTC Therapeutics, Sarepta, Scholar Rock, and Ultragenyx Pharmaceutical Inc.; and has received compensation as a member of a data and safety monitoring board (Canavan disease) for Aspa Therapeutics; speaker fees and honoraria from Avexis and Italfarmaco. K.P.B. and O.B.T. is or was an advisor/consultant for Effik/Italfarmaco group, Coave Therapeutic, AFM Scientific advisory Board, Minoryx, Inventiva, BAEM, Amstrust, and Apteus; and has received clinical trial funding from AveXis, Biogen/Ionis Pharmaceuticals, Metafora Biosystems, Roche, Sarepta, Wave Life Sciences, and Genethon. D.G. has received clinical trial funding from Metafora Biosystems. A.D., I.M., M.R., and D.C.T. report no disclosures related to the manuscript.

Funding agency: Ultragenyx Pharmaceutical Inc.

Received: 14 February 2024; **Revised:** 9 April 2024; **Accepted:** 11 April 2024

Published online 9 May 2024 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.29822

Methods: UX007G-CL301 was a randomized, double-blind, placebo-controlled, phase 3 crossover study. After a 6-week run-in, eligible patients were randomized 1:1 to the first sequence (triheptanoin/placebo or placebo/triheptanoin) titration plus maintenance, followed by washout and the opposite sequence titration plus maintenance. The placebo (safflower oil) matched the appearance, taste, and smell of triheptanoin. Open-label triheptanoin was administered in the extension. The frequency of disabling paroxysmal movement disorder events per 4 weeks (recorded by diary during maintenance; primary endpoint) was assessed by Wilcoxon rank-sum test.

Results: Forty-three patients (children, n = 16; adults, n = 27) were randomized and treated. There was no difference between triheptanoin and placebo in the mean (interquartile range) number of disabling paroxysmal movement disorder events (14.3 [4.7–38.3] vs. 11.8; [3.2–28.7]; Hodges-Lehmann estimated median difference: 1.46; 95% confidence interval, −1.12 to 4.36; $P = 0.2684$). Treatment-emergent adverse events were mild/moderate in severity and included diarrhea, vomiting, upper abdominal pain, headache, and nausea. Two patients discontinued the study because of non-serious adverse events that were predominantly gastrointestinal. The study was closed early during the open-label extension because of lack of effectiveness. Seven patients continued to receive triheptanoin compassionately.

Conclusion: There were no significant differences between the triheptanoin and placebo groups in the frequency of disabling movement disorder events during the double-blind maintenance period.

Key Words: glucose transporter type 1 deficiency syndrome; paroxysmal movement disorder; phase 3; triheptanoin; UX007

Glucose transporter type 1 deficiency syndrome (Glut1DS) is a rare disease in which decreased glucose transport to the brain results in cerebral energy deficiency and impaired brain development and function.[1-5] Glut1DS is phenotypically broad and varies by age of onset from severe, infantile-onset, developmental, and epileptic encephalopathy to mild movement disorders in adults.[4,6-8]

Movement disorders in Glut1DS can be persistent (eg, dystonia, ataxia, and tremor) or paroxysmal, with symptoms of varying duration and severity (eg, dyskinesia, major motor dysfunction, and neurological symptoms).[7-13] Paroxysmal movement disorders are often elicited by a triggering event, such as fasting or exercise. Ketogenic diets (KD) have may provide benefit for epilepsy, movement disorders, and cognitive symptoms, but not all patients with Glut1DS respond to or tolerate a KD.[7-9,14-18]

Triheptanoin is a triglyceride composed of three heptanoate (C7 fatty acid) esters and is metabolized to heptanoate, and further to the tricarboxylic acid cycle precursors propionyl-CoA and acetyl-CoA and 4- and 5-carbon ketone bodies, which are energy sources for the brain.[19-21] In an open-label, phase 2 pilot study in patients with Glut1DS not receiving a KD treatment with triheptanoin led to significant and sustained decreases in non-epileptic paroxysmal manifestations.[22,23] A small group of patients with Glut1DS manifesting persistent paroxysmal events while on a KD successfully transitioned to triheptanoin.[24] In open-label phase 2 studies in patients with long-chain fatty acid disorders, treatment with triheptanoin reduced the rate of major clinical events and improved exercise tolerance and/or health-related quality of life versus pre-treatment periods.[25-27] However, in a randomized, double-blind phase 2 study, treatment with triheptanoin, compared with safflower oil placebo, did not significantly reduce seizure frequency in patients with Glut1DS not on a KD.[28] Therefore, we designed a phase 3 study that assessed the effectiveness and safety of triheptanoin in reducing the frequency of disabling paroxysmal movement disorder events in patients with Glut1DS on a supervised regular diet.

Methods

Study Design and Participants

This randomized, double-blind, placebo-controlled, phase 3 crossover study (ClinicalTrials.gov, NCT02960217; EudraCT, 2015-005536-17) was conducted at 12 centers in the United States, United Kingdom, Spain, Italy, Germany, and France. The objectives were to evaluate the effectiveness and safety of triheptanoin for the treatment of disabling paroxysmal movement disorders associated with Glut1DS.

In the 6-week run-in period, disabling paroxysmal movement disorder events were recorded by patients/caregivers in a daily electronic Glut1DS symptom diary (Supplementary Fig. S1). The run-in period could be extended for patient adjustment to an isocaloric diet and the dietary schedule. If the minimum number of events was not met or if the patient completed <80% of the daily symptom diary, the entry was deemed a screen failure. Enrolled patients were then randomized to one of two double-blind treatment sequences (triheptanoin/safflower oil placebo or safflower oil placebo/triheptanoin) in treatment period 1 (2-week

titration plus 8-week maintenance). After a 2-week washout, patients crossed over to the second randomized, double-blind treatment sequence (safflower oil placebo to triheptanoin and triheptanoin to safflower oil placebo) in treatment period 2 (2-week titration plus 8-week maintenance). After completing the 22-week double-blind period, patients could optionally enter the open-label extension to receive triheptanoin for up to 3 years or until triheptanoin was commercially available.

Key eligibility criteria were age ≥6 years; genetically confirmed Glut1DS; ≥8 disabling paroxysmal movement disorder events in the 12 weeks before screening or ≥6 disabling paroxysmal movement disorder events in any six consecutive weeks during the last 12 weeks before screening; ≥4 disabling paroxysmal movement disorder events in the first 6 weeks of the run-in period; ≥80% completion of the daily Glut1DS symptom diary during the run-in period; non-fasting plasma concentration of β-hydroxybutyrate ≤1 mmol/L; tolerance of triheptanoin or safflower oil; no participation in the classic KD, modified Atkins diet, or ketosis-inducing modified-fat diet for ≥3 months before screening; and no triheptanoin or prohibited medications/supplements (medium chain triglyceride [MCT] oil, including coconut oil, KetoCal or other foods containing MCT oil, barbiturates, and pancreatic lipase inhibitors) within 30 days of screening.

The study was conducted according to the principles of the Declaration of Helsinki and International Council for Harmonization Good Clinical Practice guidelines. The study protocol was approved by the institutional review board or ethics committee at each site. Prior written, informed consent was given by all patients or their legal representatives.

Randomization and Masking

Patients were randomly assigned 1:1 to one of two groups using an Interactive Web Randomization System using a schedule developed by a third-party vendor to maintain blinding. The sponsor, patients, and site personnel were blinded to treatment until the open-label extension.

Study Procedures

During the double-blind period, dosing in either schedule was titrated for 2 weeks until the patient reached their age-related target dose equivalent to 25% to 35% of total daily caloric intake (Supplementary Table S1).[19,20,29] If the target dose was not reached, titration continued until the maximum tolerated dose was reached. The age-related target dose of triheptanoin (a colorless to yellow oil) was mixed into food/drink/formula and administered orally in ≥4 doses/day. Safflower oil (placebo) is a long-chain fat matching the appearance, taste, and smell of triheptanoin. The safflower oil dose, titration, and mode of administration were identical to those of triheptanoin.

Triheptanoin/placebo were dispensed/shipped to patients; patients/caregivers recorded consumption daily. Empty containers were returned during site visits. Concomitant medications were allowed, except for barbiturates, pancreatic lipase inhibitors, or any supplements/medical food containing MCT oil, including coconut oil. Three-day diet diaries were completed by patients/caregivers and were reviewed continually by site dietitians to ensure an isocaloric diet. β-Hydroxybutyrate levels were monitored to detect ketosis.

Frequency and duration of disabling paroxysmal movement disorders were determined based on patient/caregiver completion of the daily electronic Glut1DS symptom diary (ERT Corporation) throughout the double-blind period and open-label extension. Diaries were reviewed by site clinicians. A movement disorder event was defined as the time during which the patient experienced ≥1 movement disorder symptom, including symptoms occurring during a single movement disorder event or the significant worsening of continuous movement disorders. A movement disorder event was considered disabling if it affected the patient's physical functioning and daily activities.

Daytime (10 AM–8 PM) and nighttime (12 AM–5 AM) activity were measured by actigraphy (Actigraph GT9X Link). To potentially elicit more paroxysmal events, trained clinicians used the 12-minute walk test (12MWT) to evaluate endurance and walking capacity per the 6-minute walk (6MWT) test guidelines.[30-32] Patient/caregiver global impression of severity at baseline and change in clinical status was assessed using the Clinical Global Impression of Severity (CGI-S) and Improvement (CGI-I) scales[33]: 1, normal; 2, mild; 3, moderate; and 4, severe. The CGI-I scale indicated the degree of improvement/worsening: 1, very much better; 2, much better; 3, a little better; 4, no change; 5, a little worse; 6, much worse; 7, very much worse. Severity and change in clinical status were assessed by physicians using the CGI-S and CGI-I scales. Scores used by physicians were identical to those described for the patient/caregiver.

Patient well-being was reported by patients/caregivers using the Patient-Reported Outcomes Measurement Information System (PROMIS) assessing physical function, fatigue, pain interference, sleep, cognitive functioning, and social health based on age.[34] Neuropsychological function was assessed by a trained clinician using the Cambridge Neuropsychological Test Automated Battery (CANTAB).[35] Patients/caregivers reported performance and satisfaction of activities related to self-care, leisure, and productivity using the

Canadian Occupational Performance Measurement (COPM).[36]

Plasma concentrations of the triheptanoin metabolites β-hydroxybutyrate, β-hydroxypentanoate, C7-carnitine (L-heptanoylcarnitine), and heptanoate were assessed using validated methods. All adverse events (AEs) were recorded and graded using National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Clinical and laboratory assessments were performed at all study visits.

Statistical Analysis

It was estimated that patients who received placebo or triheptanoin would experience a mean of 8 or 4, respectively, disabling paroxysmal movement disorders per 4 weeks, with a standard deviation (SD) of the difference of 7.4. Assuming a discontinuation rate of 15%, a sample size of 40 patients (20 per treatment sequence) was estimated to have ≥85% power to detect between-group differences in the mean number of paroxysmal movement disorders per 4 weeks.

Endpoints were analyzed for patients who received study drug. The primary endpoint was the frequency of disabling paroxysmal movement disorders, assessed as movement disorder events observed during the maintenance period, as recorded by patients/caregivers in the daily Glut1DS symptom diary. Secondary endpoints were patient-reported duration of disabling paroxysmal movement disorders during the maintenance period, walking capacity (12MWT), patient/caregiver CGI-I, health-related quality of life (PROMIS questionnaire), and cognitive function (CANTAB). Exploratory endpoints included pharmacokinetics of triheptanoin metabolites; occupational performance measures (COPM); physician CGI-S and CGI-I; and activity levels using a wrist-worn actigraphy device. Safety endpoints included AEs and clinically significant changes in vital signs, clinical laboratory tests, and electrocardiogram.

Effectiveness endpoints were assessed for normality using the Wilk Shapiro test. If the normality assumption was not met (P-value <0.05), the Wilcoxon rank-sum test was used to assess treatment difference in the endpoint, with the Hodges-Lehmann estimate (with 95% confidence interval [CI]) of the location shift. If the normality assumption was met (Wilk Shapiro P-value ≥0.05), the endpoint was assessed using an analysis of covariance (ANCOVA) model with study baseline endpoint value as covariate, treatment sequence and group as fixed effects, and patient as random effect within the sequence. Movement disorder event frequency and duration analyses were weighted using the number of non-missing days divided by 8 weeks (ie, the maintenance period duration).

Actigraphy results were analyzed with weighted linear mixed models of two-period (ie, treatment periods 1 and 2) and three-period (ie, run-in period plus treatment periods 1 and 2) data sets, with treatment, period, and treatment sequence as fixed effects and patient as random effect (Koneksa Health). Because the normality assumption was not met, the likelihood ratio test (LRT) was used to obtain empirical P-values for regression coefficients and parametric bootstrap with 200 simulations.

Pharmacokinetics and safety data were summarized descriptively.

Results

Patients

Between April 19, 2017 and February 23, 2018, 44 patients were randomized to treatment (Fig. 1). The study population included 16 children and 27 adults with genetically confirmed Glut1DS and was 55.8% female and 79.1% white (Table 1). Baseline symptoms of Glut1DS included cognitive impairment/delay (74.4%), walking/gait abnormalities (74.4%), paroxysmal exertional dyskinesia (72.1%), ataxia (69.8%), seizures (69.8%), and dystonia (65.1%). Most patients had previously received a prescribed high-fat diet (classic KD, 51.2%; modified Atkins diet, 11.6%).

Forty-three patients received triheptanoin and were included in the analysis. Thirty-eight (86%) patients completed the double-blind period, and 33 entered the open-label extension, three of whom subsequently discontinued treatment (lack of effectiveness, n = 2; AE, n = 1) (Fig. 1). The remaining 29 patients were withdrawn by the sponsor on October 9, 2019, when the study was closed early because of lack of effectiveness.

Treatment Compliance, Exposure, and Pharmacokinetics

Mean (SD) treatment compliance ([product received during treatment period/product expected during same treatment period] × 100) was 91.8% (9.6%) for placebo and 87.7% (16.3%) for triheptanoin during the double-blind period and 86.4% (14.4%) for triheptanoin during the open-label extension. During the double-blind period, the minimum target dose (25% daily caloric intake) was reached by 41 (95.3%) patients with triheptanoin and by 37 (86.0%) patients with placebo. The mean (SD) maximum daily caloric intake achieved was 31.2% (5.0%) for triheptanoin and 30.4% (8.7%) for placebo. The mean (SD) duration of triheptanoin treatment was 65.7 (12.1) days during the double-blind period, 305.0 (122.7) days during the open-label extension, and 299.8 (172.6) days overall.

The most common concomitant medications throughout the study were analgesics (34.9%), antibacterial products (20.9%), anti-inflammatory and antirheumatic

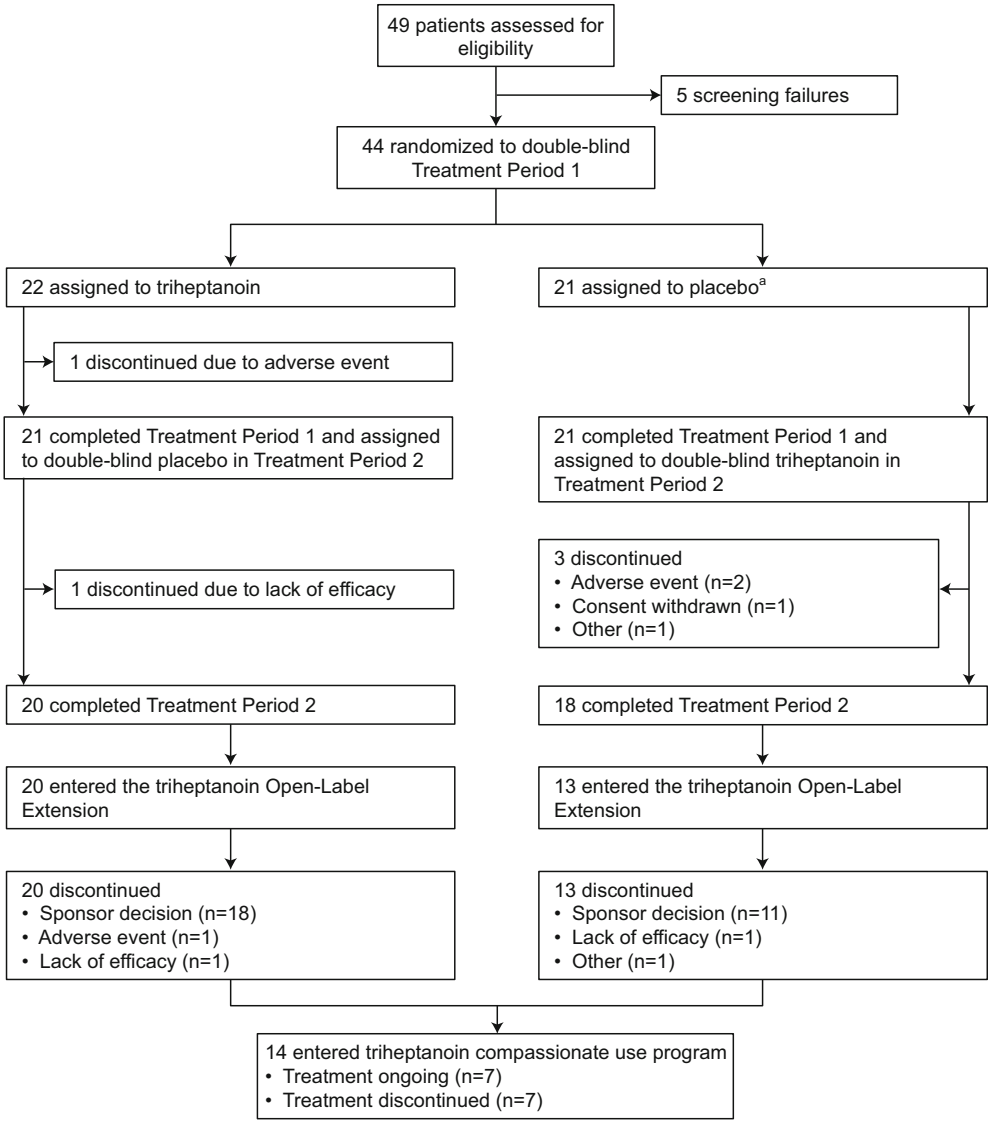

FIG. 1. Study disposition. [a]One patient discontinued before receiving treatment because of ineligibility.

products (18.6%), and antiseizure medications (16.3%; Supplementary Table S2). There were no apparent interactions between triheptanoin and antiseizure medications.

Using plasma collected at study week 34 of the open-label extension, mean concentrations of the triheptanoin metabolites acyl carnitine, β-hydroxybutyric acid, β-hydroxypentanoic acid, and heptanoic acid peaked by 30 to 90 minutes after dosing and gradually declined until 120 minutes after dosing (Supplementary Table S3).

Effectiveness

There was no significant difference between the triheptanoin and placebo groups in the frequency of movement disorder events during double-blind maintenance, as recorded by patients/caregivers in the daily Glut1DS symptom diary (Fig. 2). The median (interquartile range) number of movement disorder events per 4 weeks was 14.3 (4.7–38.3) with triheptanoin versus 11.8 (3.2–28.7) with placebo (Hodges-Lehmann estimated median difference, 1.46; 95% CI, −1.12 to 4.36; $P = 0.2684$) (Supplementary Table S4). During the open-label extension, the frequency of movement disorder events was generally stable until study week 58 and decreased thereafter as the number of patients with available data decreased (Fig. 2). Seven patients who experienced a variety of symptoms at study baseline and varying degrees of improvement during the study continued to receive triheptanoin compassionately (Fig. 1, Supplementary Fig. S2); effectiveness data for these patients are unavailable.

TABLE 1 *Demographics and baseline disease characteristics*

	Triheptanoin/ placebo (n = 22)	Placebo/ triheptanoin (n = 21)	Total (N = 43)
Mean (SD) age, years	23.4 (13.2)	18.4 (5.7)	21.0 (10.4)
<18 years, n (%)	7 (31.8)	9 (42.9)	16 (37.2)
≥18 years, n (%)	15 (68.2)	12 (57.1)	27 (62.8)
Mean (SD) age at Glut1DS diagnosis, years	18.4 (14.9)	12.3 (6.1)	15.4 (11.7)
Sex, n (%)			
Male	10 (45.5)	9 (42.9)	19 (44.2)
Female	12 (54.5)	12 (57.1)	24 (55.8)
Race, n (%)			
White	18 (81.8)	16 (76.2)	34 (79.1)
Black	0	1 (4.8)	1 (2.3)
Missing	4 (18.2)	4 (19.0)	8 (18.6)
Prescribed diet plan history, n (%)			
Classic ketogenic	10 (45.5)	12 (57.1)	22 (51.2)
Modified Atkins	1 (4.5)	4 (19.0)	5 (11.6)
None	11 (50.0)	5 (23.8)	16 (37.2)
Reason for prescribed diet plan discontinuation, n (%)			
Noncompliance	9 (40.9)	6 (28.6)	15 (34.9)
Lack of effectiveness	3 (13.6)	6 (28.6)	9 (20.9)
Side effects	3 (13.6)	3 (14.3)	6 (14.0)
Other	2 (9.1)	3 (14.3)	5 (11.6)
Mean (SD) movement disorder frequency, events/4 weeks	34.2 (43.5)	23.1 (21.2)	28.8 (34.5)
Glut1DS symptoms, n (%)			
Cognitive impairment or delay	17 (77.3)	15 (71.4)	32 (74.4)
Walking/gait abnormalities	18 (81.8)	14 (66.7)	32 (74.4)
Paroxysmal exertional dyskinesia	16 (72.7)	15 (71.4)	31 (72.1)
Ataxia	13 (59.1)	17 (81.0)	30 (69.8)
Seizures	15 (68.2)	15 (71.4)	30 (69.8)
Dystonia	16 (72.7)	12 (57.1)	28 (65.1)
Dysarthria	11 (50.0)	16 (76.2)	27 (62.8)
Dyspraxia	12 (54.5)	9 (42.9)	21 (48.8)
Spasticity	11 (50.0)	9 (42.9)	20 (46.5)
Abnormal eye movements	9 (40.9)	10 (47.6)	19 (44.2)
Delayed motor development	10 (45.5)	9 (42.9)	19 (44.2)
Hypotonia	7 (31.8)	12 (57.1)	19 (44.2)
Tremor	10 (45.5)	6 (28.6)	16 (37.2)
Myoclonus	5 (22.7)	6 (28.6)	11 (25.6)

(Continues)

TABLE 1 *Continued*

	Triheptanoin/ placebo (n = 22)	Placebo/ triheptanoin (n = 21)	Total (N = 43)
Aggressive, impulsive, or hyperactive behavior	7 (31.8)	1 (4.8)	8 (18.6)
Chorea/choreoathetosis	6 (27.3)	2 (9.5)	8 (18.6)
Microcephaly	5 (22.7)	3 (14.3)	8 (18.6)
SLCA1 mutation type, n (%)			
Missense	14 (63.6)	16 (76.2)	30 (69.8)
Frameshift	1 (4.5)	2 (9.5)	3 (7.0)
Stop gained	3 (13.6)	0	3 (7.0)
Deletion	1 (4.5)	2 (9.5)	3 (7.0)
Start lost	1 (4.5)	1 (4.8)	2 (4.7)
Insertion	1 (4.5)	0	1 (2.3)
Splice acceptor	0	1 (4.8)	1 (2.3)

Abbreviations: SD, standard deviation; Glut1DS, glucose transporter type 1 deficiency syndrome; *SLCA1*, Solute Carrier Family 2 Member 1.

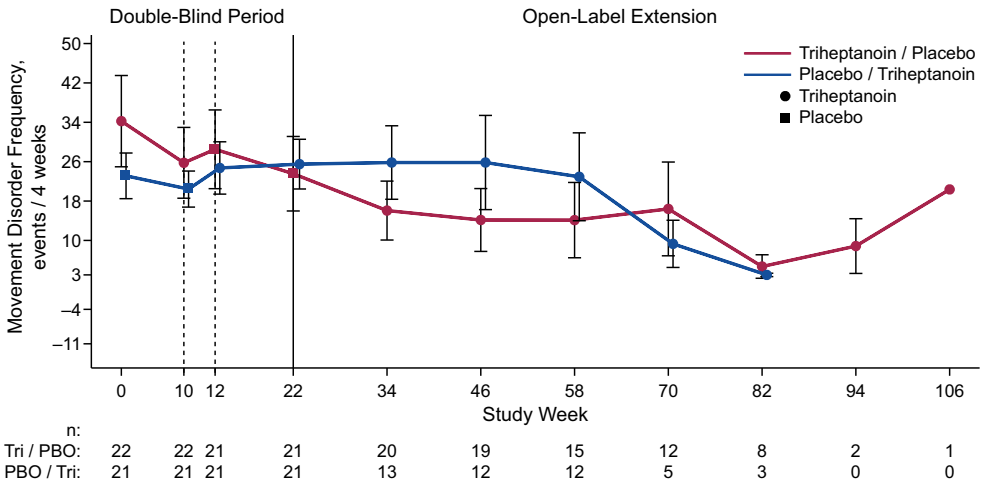

FIG. 2. Change in mean (standard error) movement disorder frequency over time during the double-blind treatment period and the open-label extension. Patient numbers based on initial treatment sequence randomization are shown beneath the graph. Movement disorder frequency was normalized to a 4-week rate during each period. Dashed lines indicate washout period. PBO, placebo; Tri, triheptanoin.

The mean (SD) total duration of movement disorders increased from 14.2 (35.1) hours per 4 weeks at baseline to 24.3 (67.1) hours per 4 weeks with triheptanoin during the maintenance period and from 14.2 (35.1) to 25.6 (91.1) hours per 4 weeks with placebo. The duration of movement disorders was significantly shorter in the triheptanoin group than in the placebo group (mean [SD], 24.3 [67.1] vs. 25.6 [91.1] hours/4 weeks; Hodges-Lehmann estimated median difference, 0.87; 95% CI, −0.01 to 2.92; $P = 0.0497$) (Supplementary Table S4).

The 12MWT distance walked during the double-blind period and open-label extension is summarized in Supplementary Figure S3. There was no significant difference between the triheptanoin and placebo groups in the change from baseline to week 10 in 12MWT distance walked (Hodges-Lehmann estimated median difference, 25.00; 95% CI, −62.5 to 91.5; $P = 0.6419$). Assessment of between-group differences in 12MWT distance walked during the open-label extension was limited by small sample sizes.

During the double-blind period, mean CGI-I scores ranged from "a little better" to "no change" in both treatment groups when reported by patients/caregivers or by physicians (Supplementary Figs. S4A and S2B). There was no significant difference between the triheptanoin and placebo groups CGI-I at study week 10 when reported by patients/

caregivers (ANCOVA least-squares mean difference, −0.1; 95% CI, −0.6 to 0.5; $P = 0.8329$) or by physicians (Hodges-Lehmann estimated median difference, 0.5; 95% CI, 0–1.0; $P = 0.1982$). Mean CGI-S scores reported by physicians during the double-blind period ranged from mild to moderate (Supplementary Fig. S4C) and were likewise not significantly different between the triheptanoin and placebo groups (Hodges-Lehmann estimated median difference, 0; 95% CI, 0–0; $P = 0.3877$). Evaluation of CGI-I and CGI-S scores during the open-label extension was limited by small sample sizes.

At week 10 of the double-blind period, there were no significant differences between the triheptanoin and placebo groups in any PROMIS domains for the assessment of health-related quality of life (Supplementary Table S5), the CANTAB domains for the assessment of cognitive function (Supplementary Table S6), or in the COPM performance or satisfaction scores (Supplementary Table S7). Assessment of between-group differences in COPM scores during the open-label extension was limited by small sample sizes (Supplementary Fig. S5).

Wristband actigraphy data were available for 31 patients. Mean nighttime activity was low, with no effect by sequence, and did not significantly differ between the triheptanoin and placebo groups (Table 2, Supplementary Fig. S6). Compared with the placebo group, the triheptanoin group had reduced mean daytime activity (2-period LRT, −2.01; 2-period $P = 0.055$; 3-period LRT, −1.91; 3-period $P = 0.056$) and significantly reduced percentage of time in moderate or higher activity (2-period LRT, −4.24; 2-period $P = 0.005$; 3-period LRT, −4.24; 3-period $P = 0.005$) (Table 2).

Safety

During the double-blind period, treatment-emergent AEs (TEAEs) occurred more frequently with triheptanoin (n = 40; 93.0%) than placebo (n = 34; 81.0%), and treatment-related AEs (TRAEs) were more frequent with triheptanoin (n = 33; 76.7%) than placebo (n = 19; 45.2%) (Table 3). During the open-label extension, 28 (84.8%) patients had TEAEs and 17 (51.5%) had TRAEs. Overall, 40 (93.0%) patients who received triheptanoin TEAEs and 34 (79.1%) had TRAEs.

Most TEAEs were mild or moderate (grade 1 or 2) in severity. Five (11.6%) patients who received triheptanoin had grade 3 TEAEs; no grade 4 or fatal TEAEs were reported. Three patients had serious TEAEs while receiving triheptanoin, all of which resolved. The first patient had serious, grade 3 subcontinuous movement disorders during the double-blind period that were considered possibly related to treatment and during the open-label extension that were considered unlikely related to treatment. The second patient had serious, grade 3 head trauma during the double-blind period that was considered unrelated to treatment. The third patient had serious, grade 2 lower limb asymmetry during the open-label extension that was considered unrelated to treatment.

The most frequent (occurring in ≥20% of patients) TEAEs among patients who received triheptanoin were diarrhea (53.5%), vomiting (37.2%), upper abdominal pain (34.9%), headache (25.6%), and nausea (23.3%). The most frequent TRAEs among patients who received triheptanoin were diarrhea (41.9%), vomiting (32.6%), and upper abdominal pain (32.6%) (Table 3). During the double-blind period, gastrointestinal TEAEs were more frequent among patients who received triheptanoin than placebo (74.4% vs. 40.5%) (Supplementary Table S8). The incidence of gastrointestinal TEAEs was 54.5% in the open-label extension and 79.1% among patients overall who received triheptanoin.

Two patients discontinued triheptanoin and left the study because of non-serious AEs (patient one:

TABLE 2 *Difference between triheptanoin and placebo groups in actigraphy results*

Time in moderate or higher activity, %	Estimate (SE)	LRT	*P*-value[a]
Treatment periods 1 and 2	−1.46 (0.34)	−4.24	0.005
Run-in period + treatment periods 1 and 2	−1.74 (0.41)	−4.24	0.005
Mean daytime activity			
Treatment periods 1 and 2	−68.96 (34.29)	−2.01	0.055
Run-in period + treatment periods 1 and 2	−78.41 (41.13)	−1.91	0.056
Mean nighttime activity			
Treatment periods 1 and 2	0.46 (11.76)	0.04	0.95
Run-in period + treatment periods 1 and 2	9.92 (14.09)	0.70	0.49

Abbreviations: SE, standard error; LRT, likelihood ratio test.
[a]The residuals from the 2-period and 3-period models did not meet the normality assumption (Wilk–Shapiro test *P*-value <0.05); bootstrap *P*-values were used.

TABLE 3 *Adverse events*

	Double-blind treatment period		OLE triheptanoin (n = 33)	Overall triheptanoin (N = 43)
	Placebo (n = 42)	Triheptanoin (n = 43)		
Patients with a TEAE, n (%)	34 (81.0)	40 (93.0)	28 (84.8)	40 (93.0)
Patients with a TRAE, n (%)	19 (45.2)	33 (76.7)	17 (51.5)	34 (79.1)
Patients with a serious TEAE, n (%)	1 (2.4)	2 (4.7)	2 (6.1)	3 (7.0)
Patients with a serious TRAE,[a] n (%)	0	1 (2.3)	0	1 (2.3)
Patients with a grade 3/4 TEAE, n (%)	3 (7.1)	4 (9.3)	3 (9.1)	5 (11.6)
Patients with a fatal TEAE, n (%)	0	0	0	0
TRAEs occurring in ≥10% of patients, n (%)				
Diarrhea	4 (9.5)	17 (39.5)	6 (18.2)	18 (41.9)
Vomiting	4 (9.5)	11 (25.6)	6 (18.2)	14 (32.6)
Upper abdominal pain	6 (14.3)	13 (30.2)	7 (21.2)	14 (32.6)
Nausea	4 (9.5)	5 (11.6)	3 (9.1)	7 (16.3)
Abdominal pain	1 (2.4)	6 (14.0)	2 (6.1)	6 (14.0)

Abbreviations: OLE, open-label extension; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.
[a]A serious adverse event was defined as an adverse event leading in any of the following outcomes: death, life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant incapacity or disability, or a congenital anomaly/birth defect.

treatment-related upper abdominal pain, aggressive behavior, headache, and vomiting; patient two: possibly treatment-related abdominal pain and diarrhea). Sixteen patients had triheptanoin dose modifications because of AEs (dose reductions, n = 14; dose increases, n = 2), and six patients had dose interruptions because of AEs. Most AEs leading to dose modifications were mild to moderate gastrointestinal events considered by the investigators to be at least possibly or probably related to treatment with triheptanoin.

Discussion

This randomized, double-blind, placebo-controlled phase 3 study was closed early due to lack of effectiveness because of the lack of significant differences between the triheptanoin and placebo groups in the frequency of movement disorder events during the double-blind maintenance period. During the open-label extension, the frequency of movement disorder events remained generally stable until patient numbers declined. Seven patients continued to receive triheptanoin in the compassionate use program. Unfortunately, no similar controlled trials of a KD for movement disorder frequency and duration in Glut1DS are available for comparison with our findings. In a randomized, double-blind, placebo-controlled phase 2 study (N = 36), treatment with triheptanoin at a target dose of 35% of caloric intake for 8 weeks did not significantly reduce the frequency of seizures in Glut1DS patients receiving a standard diet.[28]

The safety profile of triheptanoin in this study is consistent with that reported in other studies of triheptanoin in Glut1DS and long-chain fatty acid disorders.[22,23,25,26,28,37] No new safety concerns were identified. Gastrointestinal AEs were the most frequent type of AE, occurred more frequently with triheptanoin than placebo (74.4% vs. 40.5%) during the double-blind period, were typically mild to moderate in severity, and were most often the reason for triheptanoin dose modifications or interruptions. Two patients discontinued the study because of AEs that were predominantly gastrointestinal (upper abdominal pain, diarrhea, vomiting, aggressive behavior, and headache).

Several factors could have contributed to the failure to meet the primary endpoint. As with the KD, the effectiveness of triheptanoin is dependent on appropriate dietary instructions, patient compliance with the prescribed triheptanoin dosage and low-sugar diet, and careful monitoring of sugar intake.[22,23] β-Hydroxybutyrate levels were assessed for the detection of ketosis and body weight and adherence to a nutritionally balanced isocaloric diet were monitored regularly by study dietitians. Nevertheless, dietary design and noncompliance remained a possible departure from protocol. Patients and caregivers were instructed to avoid simple sugars at the end of the

inclusion period (December 2017); therefore, sugar intake was not strictly monitored. Persistence of paroxysmal movement events during treatment with triheptanoin has been attributed to consumption of simple sugars by some patients.[23,24] Therefore, it is possible that stricter control of sugar intake during this study may have resulted in greater triheptanoin efficacy. However, this speculation is based on open-labelled studies that were not confirmed by randomized, blinded, placebo-controlled studies.

The selection of safflower oil as a placebo may have been an additional limitation in this study. An oil was selected for blinding because triheptanoin must be mixed with food by the patient/caregiver, and oils have distinct and easily recognized viscosity and texture. However, it could be argued that any oil, in a condition such as Glut1DS that may respond to additional dietary fat, may have a treatment effect, and therefore, may not function as a true placebo.

The cross-over design, which was chosen because of the complexity and heterogeneity of paroxysmal movement disorders in Glut1DS,[7] may not have been appropriate for assessing the primary endpoint. It is possible that intrinsic limitations of the selected clinical assessments may also have contributed to the lack of difference between the triheptanoin and placebo in the other effectiveness endpoints. For example, the 12MWT, despite being more demanding the 6MWT, may not have been sufficient to elicit exercise-induced dyskinesia in some patients. Furthermore, a larger number of patients might have improved the between-group statistical comparisons in this study. In hindsight, a longer randomized study period (ie, 6 months) and longer washout period may have minimized time-based sensitivity issues with outcomes and provided additional time for dietary adaptation. A greater dose of triheptanoin and the allowance of personalized adjustments in triheptanoin dose (to account for daily activities) or continuation of KD may have also improved treatment effectiveness. Furthermore, allowing enrollment of younger (ie, <6 years) may have provided further efficacy insight. Finally, although patients/caregivers had training in use of the daily symptom diary at screening and oversight by site personnel throughout, it is possible that inconsistent diary use by patients/caregivers may have limited the comparison of triheptanoin effectiveness between treatment groups.

In the absence of alternatives to a KD, which may be ineffective or not tolerated, early open-label uncontrolled studies of triheptanoin in Glut1DS were promising, but unfortunately, were not confirmed by our placebo-controlled randomized double blind study.[22,23] When designing future clinical studies of Glut1DS, it will be important to consider the complexity and heterogeneity of the disabling movement disorders, as well as elements of study design, such as dietary monitoring (especially simple sugar intake), sample size, and randomized treatment period length. ■

Acknowledgments: We thank the patients and their families who participated in this study. We thank Debra Geary Hook, MPH, PhDc, RD, FAND, who passed away in 2022, for her important contributions as the study dietitian. We also acknowledge the many site dietitians, clinical trial coordinators, and other site personnel for their contributions to the study. This work was funded by Ultragenyx Pharmaceutical Inc. Ben Scott, PhD (Scott Medical Communications, LLC), provided medical writing support funded by Ultragenyx Pharmaceutical Inc.

Data Availability Statement

Requests for data or the clinical study report are available to researchers providing a methodologically sound proposal in accordance with the Ultragenyx data sharing commitment. Requestors must sign a data access and use agreement. Data will be shared via secured portal. The study protocol is publicly available.

References

1. Larsen J, Johannesen KM, Ek J, et al. The role of SLC2A1 mutations in myoclonic astatic epilepsy and absence epilepsy, and the estimated frequency of GLUT1 deficiency syndrome. Epilepsia 2015;56(12):e203–e208.
2. Symonds JD, Zuberi SM, Stewart K, et al. Incidence and phenotypes of childhood-onset genetic epilepsies: a prospective population-based national cohort. Brain 2019;142(8):2303–2318.
3. Castellotti B, Ragona F, Freri E, et al. Screening of SLC2A1 in a large cohort of patients suspected for Glut1 deficiency syndrome: identification of novel variants and associated phenotypes. J Neurol 2019;266(6):1439–1448.
4. Koch H, Weber YG. The glucose transporter type 1 (Glut1) syndromes. Epilepsy Behav 2019;91:90–93.
5. Gras D, Roze E, Caillet S, et al. GLUT1 deficiency syndrome: an update. Rev Neurol (Paris) 2014;170(2):91–99.
6. De Vivo DC, Trifiletti RR, Jacobson RI, Ronen GM, Behmand RA, Harik SI. Defective glucose transport across the blood–brain barrier as a cause of persistent hypoglycorrhachia, seizures, and developmental delay. N Engl J Med 1991;325(10):703–709.
7. Klepper J, Akman C, Armeno M, et al. Glut1 deficiency syndrome (Glut1 DS): state of the art in 2020 and recommendations of the international Glut1DS study group. Epilepsia Open 2020;5(3):354–365.
8. Pearson TS, Akman C, Hinton VJ, Engelstad K, De Vivo DC. Phenotypic spectrum of glucose transporter type 1 deficiency syndrome (Glut1 DS). Curr Neurol Neurosci Rep 2013;13(4):342.
9. Alter AS, Engelstad K, Hinton VJ, et al. Long-term clinical course of GLUT1 deficiency syndrome. J Child Neurol 2015;30(2):160–169.
10. De Giorgis V, Teutonico F, Cereda C, et al. Sporadic and familial glut1ds Italian patients: a wide clinical variability. Seizure 2015;24:28–32.
11. Leen WG, Taher M, Verbeek MM, Kamsteeg EJ, van de Warrenburg BP, Willemsen MA. GLUT1 deficiency syndrome into adulthood: a follow-up study. J Neurol 2014;261(3):589–599.
12. Pons R, Collins A, Rotstein M, Engelstad K, De Vivo DC. The spectrum of movement disorders in GLUT-1 deficiency. Mov Disord 2010;25(3):275–281.
13. Klepper J, Leiendecker B, Eltze C, Heussinger N. Paroxysmal non-epileptic events in Glut1 deficiency. Mov Disord Clin Pract 2016;3(6):607–610.
14. Kass HR, Winesett SP, Bessone SK, Turner Z, Kossoff EH. Use of dietary therapies amongst patients with GLUT1 deficiency syndrome. Seizure 2016;35:83–87.

15. Ramm-Pettersen A, Nakken KO, Skogseid IM, et al. Good outcome in patients with early dietary treatment of GLUT-1 deficiency syndrome: results from a retrospective Norwegian study. Dev Med Child Neurol 2013;55(5):440–447.
16. Hao J, Kelly DI, Su J, Pascual JM. Clinical aspects of glucose transporter type 1 deficiency: information from a global registry. JAMA Neurol 2017;74(6):727–732.
17. Bekker YAC, Lambrechts DA, Verhoeven JS, et al. Failure of ketogenic diet therapy in GLUT1 deficiency syndrome. Eur J Paediatr Neurol 2019;23(3):404–409.
18. Pong AW, Geary BR, Engelstad KM, Natarajan A, Yang H, De Vivo DC. Glucose transporter type I deficiency syndrome: epilepsy phenotypes and outcomes. Epilepsia 2012;53(9):1503–1510.
19. Roe CR, Sweetman L, Roe DS, David F, Brunengraber H. Treatment of cardiomyopathy and rhabdomyolysis in long-chain fat oxidation disorders using an anaplerotic odd-chain triglyceride. J Clin Invest 2002;110(2):259–269.
20. Roe CR, Mochel F. Anaplerotic diet therapy in inherited metabolic disease: therapeutic potential. J Inherit Metab Dis 2006;29(2–3):332–340.
21. Marin-Valencia I, Good LB, Ma Q, Malloy CR, Pascual JM. Heptanoate as a neural fuel: energetic and neurotransmitter precursors in normal and glucose transporter I-deficient (G1D) brain. J Cereb Blood Flow Metab 2013;33(2):175–182.
22. Mochel F, Hainque E, Gras D, et al. Triheptanoin dramatically reduces paroxysmal motor disorder in patients with GLUT1 deficiency. Journal of neurology, neurosurgery, and psychiatry 2016; 87(5):550–553.
23. Hainque E, Gras D, Meneret A, et al. Long-term follow-up in an open-label trial of triheptanoin in GLUT1 deficiency syndrome: a sustained dramatic effect. Journal of neurology, neurosurgery, and psychiatry 2019;90(11):1291–1293.
24. Hainque E, Meneret A, Gras D, et al. Transition from ketogenic diet to triheptanoin in patients with GLUT1 deficiency syndrome. Journal of neurology, neurosurgery, and psychiatry 2020;91(4):444–445.
25. Vockley J, Burton B, Berry GT, et al. Results from a 78-week, single-arm, open-label phase 2 study to evaluate UX007 in pediatric and adult patients with severe long-chain fatty acid oxidation disorders (LC-FAOD). J Inherit Metab Dis 2019;42(1):169–177.
26. Vockley J, Burton B, Berry GT, et al. UX007 for the treatment of long chain-fatty acid oxidation disorders: safety and efficacy in children and adults following 24 weeks of treatment. Mol Genet Metab 2017;120(4):370–377.
27. Vockley J, Burton B, Berry G, et al. Effects of triheptanoin (UX007) in patients with long-chain fatty acid oxidation disorders: results from an open-label, long-term extension study. J Inherit Metab Dis 2021;44(1):253–263.
28. Striano P, Auvin S, Collins A, et al. A randomized, double-blind trial of triheptanoin for drug-resistant epilepsy in glucose transporter 1 deficiency syndrome. Epilepsia 2022;63(7):1748–1760.
29. Mochel F, Duteil S, Marelli C, et al. Dietary anaplerotic therapy improves peripheral tissue energy metabolism in patients with Huntington's disease. Eur J Hum Genet 2010;18(9):1057–1060.
30. Cooper KH. A means of assessing maximal oxygen intake. Correlation between field and treadmill testing. JAMA 1968;203(3):201–204.
31. McGavin CR, Gupta SP, McHardy GJ. Twelve-minute walking test for assessing disability in chronic bronchitis. Br Med J 1976; 1(6013):822–823.
32. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166(1):111–117.
33. Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry (Edgmont) 2007;4(7): 28–37.
34. Broderick JE, DeWitt EM, Rothrock N, Crane PK, Forrest CB. Advances in patient-reported outcomes: the NIH PROMIS((R)) measures. EGEMS (Wash DC) 2013;1(1):1015.
35. Luciana M, Nelson CA. Assessment of neuropsychological function through use of the Cambridge neuropsychological testing automated battery: performance in 4- to 12-year-old children. Dev Neuropsychol 2002;22(3):595–624.
36. Law M, Baptiste S, McColl M, Opzoomer A, Polatajko H, Pollock N. The Canadian occupational performance measure: an outcome measure for occupational therapy. Can J Occup Ther 1990;57(2):82–87.
37. Pascual JM, Liu P, Mao D, et al. Triheptanoin for glucose transporter type I deficiency (G1D): modulation of human ictogenesis, cerebral metabolic rate, and cognitive indices by a food supplement. JAMA Neurol 2014;71(10):1255–1265.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.