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Long-Term Treatment of Niemann-Pick Type C1 Disease with Intrathecal 2-Hydroxypropyl- β -Cyclodextrin

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Abstract

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AUTHOR CONTRIBUTIONS

EBK, JC, AH, AW, LL and JOK contributed to conception and design of the study, acquisition and analysis of data, and drafted a significant portion of the manuscript or figures. RS, KF and MH contributed to acquisition and analysis of data, and FDP and DO contributed to conception and design of the study, acquisition and analysis of data, and critical editing of the manuscript.

CONFLICT OF INTEREST

EBK and FDP are co-PIs on the phase 2/3 trial being supported by Vtesse, Inc. and are site investigators on this trial. EBK is a consultant for Vtesse, but has not received any consulting compensation for these roles, and has only a standard clinical trial funding contract for her site. EBK also has a small unrestricted research grant from Vtesse to fund personnel at her program to make available an umbrella protocol for expanded access for VTS-270 at multiple remote sites. FDP collaborates with Vtesse, as an official duty activity, under a Cooperative Research and Development agreement between NICHD and Vtesse to support the development of HPBCD as a therapy for NPC1. He does not receive any consulting compensation. DSO is a consultant for Vtesse and is a member of the Preclinical Scientific Advisory Board. JOK has been a consultant to Vtesse on outcome measures of motor function in ataxia, but has not received consulting compensation. No other authors have any disclosures relevant to this study.

Background—Intrathecal 2-hydroxypropyl- β -cyclodextrin (HP β CD) has been found to mobilize cholesterol, extend life, reduce cerebellar pathology and delay onset of ataxia in the mouse and cat models of Niemann-Pick disease, type C1 (NPC1), a clinically variable progressive and ultimately fatal neurodegenerative storage disorder characterized by endolysosomal accumulation of unesterified cholesterol.

Objective—In this study, the long-term effects of intrathecal HP β CD treatment for 2.5–3 years in humans with NPC were evaluated.

Methods—Three patients with NPC in different stages of progression and displaying varying disease manifestations were treated with intrathecal HP β CD (VTS-270) delivered by LP infusion through an intermediate-size patient population investigational new drug application for expanded access. Disease progression was monitored with the NPC Neurological Severity Scale (NSS) and numerous objective measures of function in 5 neurological domains typically impacted by the disease: cognitive/language, gait/balance, fine motor, swallowing and eye movement.

Results—No worsening in any domain except eye movements (vertical pursuit gain) was seen for any of the three patients, and in the other domains, improved scores on measures were seen over time for one or more patients. The NSS showed stable to slightly improved ratings.

Interpretation—These trajectories are not consistent with the typical trajectory of the disease and suggest that intrathecal HP β CD has stabilized the disease over an extended period of time, supporting the current phase 2/3 controlled registration trial with VTS-270.

Keywords

Niemann-Pick type C; lysosomal storage disorder; neurodegenerative disease; cholesterol; cyclodextrin

INTRODUCTION

Niemann-Pick disease, type C (NPC) is an autosomal recessive neurodegenerative disorder characterized by endolysosomal storage of unesterified cholesterol in brain, liver, spleen and other peripheral tissues.¹ NPC is caused by mutations in *NPC1* (90–95%) or *NPC2* (~5%) that yield deficient function of the corresponding proteins that normally bind and transport cholesterol, resulting in deficits in intracellular trafficking of cholesterol.² The incidence of NPC is estimated at about 1/100,000, although older-onset cases are likely under-ascertained.^{1,3} Age of onset ranges from birth to the eighth decade, with a highly heterogeneous phenotype including psychiatric, neurological, hearing, pulmonary, and visceral signs that vary depending on age of presentation, with hepatosplenomegaly more prevalent in perinatal- and infantile-onset forms, and psychiatric disease more common in teenage- and adult-onset cases.^{4–7} The classic juvenile form of NPC involves insidious onset in mid-childhood of vertical supranuclear gaze palsy (VSGP), clumsiness, cognitive decline and/or fine motor impairments evolving to overt dementia, ataxia, intention tremor, dystonia, spasticity, dysarthria, dysphagia, hearing loss, seizures and gelastic cataplexy.⁵ NPC is relentlessly progressive with death in childhood-onset cases typically in the teens or early twenties, and slower progression of later-onset cases. Diagnosis⁸ is through filipin staining

of fibroblasts, *NPC1* and *NPC2* sequencing, measurement of blood oxysterols or a diagnostic bile acid.⁹ Increasingly, cases are ascertained by exome sequencing.⁸

There are no FDA-approved therapies for NPC. Miglustat, which inhibits glucosylceramide synthesis and slows lipid accumulation in NPC models, showed improvement in horizontal saccades, swallowing, and slowing of gait deterioration in a single controlled trial in NPC1¹⁰ and slowed progression in several open-label trials.¹⁰⁻¹³ Miglustat is approved for use in NPC in multiple countries and often used off-label in the USA, but it has relatively low efficacy, and there is a clear unmet need for more effective treatments.

2-hydroxypropyl- β -cyclodextrin (HP β CD), an FDA-approved excipient used to dissolve steroids for intravenous administration, mobilizes and reduces stored cholesterol in NPC1 cellular, mouse¹⁴⁻¹⁶ and cat¹⁷ models. In the NPC1 cat, intrathecal (IT) HP β CD (only about 0.1% HP β CD crosses the blood–brain barrier) substantially reduced Purkinje cell loss, delayed neurological progression and resulted in an 8-fold prolongation of life. An 18-month open-label phase 1/2a trial¹⁸ delivering monthly lumbar IT HP β CD to 14 participants with NPC showed slowing of disease progression on the NPC Neurological Severity Scale (NSS) compared to matched natural history cohorts.¹⁹ The NSS for the 14 participants treated monthly with doses ranging from 200–900 mg increased by 1.22 ± 0.34 points per year compared to 2.92 ± 0.27 points per year ($p=0.0002$) for a 21 patient age- and disease severity-matched natural history comparison group.¹⁸ Significantly decreased progression was observed for NSS domains of ambulation, cognition and speech. Seven patients in the treated group showed no progression or mild improvement, while all the natural history cohort patients progressed within the 18 month time frame.¹⁸ Dose sensitive mid-to-high frequency hearing loss was seen in most patients, with more hearing loss in patients who did not have substantial hearing loss from their NPC and minimal, if any, hearing loss in those with moderate-severe hearing loss at baseline from their NPC.¹⁸ Biomarker assays in the phase 1/2a trial showed release of brain-derived 24(S)-hydroxycholesterol (24(S)-HC)²⁰ into CSF and blood following HP β CD infusions and reduction of elevated fatty acid binding protein 3 and calbindin D levels during treatment, demonstrating target engagement and decreased neuronal damage.¹⁸

A few patients have also been treated with HP β CD through expanded access based on individual investigational new drug (IND) approvals.²¹⁻²⁴ One mildly affected patient treated with IT HP β CD at a dose of 200 mg for 14 months was reported to have minimal very high frequency hearing loss, stabilization of disease progression with a 1-point decrease in the NSS, and release of (24(S)-HC) into blood following HP β CD infusions relative to a saline infusion baseline.²³ A review of published abstracts and papers about patients treated for 2–6 years through expanded access with IV, IT or IV/IT cyclodextrin (IT dose 200–600 mg) throughout the world revealed evaluable data from 13 patients, 12 with a clinical efficacy measure, and suggested clinical benefit or a stabilization of NPC progression in most patients, perhaps more so in mildly affected patients, and some hearing loss in 4 patients.²⁴ We report here results from three patients treated with IT HP β CD via expanded access through an intermediate-size patient population IND. Limited data including NSS scores, dosing and adverse events for the first 18 months of treatment for these patients was reported with the phase 1/2a trial,¹⁸ but here we present much more detail on long-term impact (over

2.5–3 years) on disease course, including results from evaluation of multiple neurological domains through repeated administration of a novel battery of objective measures.

PATIENTS AND METHODS

Patients

Patient 001-01 had a normal birth and typical development, but showed progressive decline in school work from age 6 years, despite special education support. At age 9 she began to have partial and secondarily generalized seizures that rapidly became intractable, despite trials of multiple medications, a vagal nerve stimulator and the ketogenic diet. At age 11 she underwent epilepsy surgery and brain pathology revealed a lysosomal storage disease. Genetic testing revealed compound heterozygosity for two known pathogenic mutations in *NPC1* (Table 1). After diagnosis, she started miglustat, which seemed to result initially in slight improvement in visual tracking; however, there was clear progression of swallowing difficulties on Miglustat with intermittent vomiting and choking on solids and liquids, as well as ongoing cognitive and language regression with a paucity of speech, significant gait apraxia, VSGP, mild hearing loss and about 1–3 seizures daily. At age 13 she screened for the phase 1/2a trial of IT HP β CD but was ineligible due to multiple anticonvulsants and vagal nerve stimulator use. She was being treated with miglustat 200 mg TID, felbamate 1800 mg BID, oxcarbazepine 1200 mg BID, clonazepam 1 mg qHS when she began treatment with HP β CD through expanded access. She has remained on Miglustat to the present, and anticonvulsants were adjusted as clinically indicated during treatment with HP β CD.

Patient 001-02 had normal birth, development and school performance until age 13, when he began to struggle more with schoolwork. *NPC1* gene testing done due to diagnosis of his sister revealed compound heterozygosity for the same mutations (Table 1). He started miglustat shortly after diagnosis, without specific improvement and with decreasing IQ while on Miglustat such that neuropsychological testing at age 14 showed borderline impairment in IQ and multiple cognitive subdomains, while retesting at age 15 showed mild decrement in cognitive scores, into the upper end of the mild impairment range. His neurological exam showed only a very subtle VSGP. He was not able to enter the phase 1/2a trial. He was taking miglustat 200 mg TID when HP β CD was initiated through expanded access, and has remained on Miglustat to the present.

Patient 001-03 had normal birth, development and school performance until age 9, when parents noted changes in gross motor skills while playing basketball, followed by intention tremor and head titubation; tutoring was needed to complete schoolwork. By age 11 she was receiving poor grades despite hard work/tutoring and became increasingly poorly coordinated. Psychological testing done at ages 11, 12, 15 and 16 revealed IQ scores in the 80s or 90s, with slow processing speed, language deficits, memory deficits, and impaired motor performance with slurred speech and hand tremor. An MRI showed cerebellar atrophy. At age 16 she was seen at the Mayo clinic with VSGP, mild ataxia, dysmetria and dysarthria and was diagnosed with NPC through abnormal cholesterol esterification, filipin staining and gene testing showing compound heterozygosity for *NPC1* mutations expected to be pathogenic (Table 1). 001-03 could not enter the phase 1/2a trial of HP β CD as it was

closed when the family requested screening. She was treated with miglustat 200 mg TID for approximately 8 months prior to initiation of HP β CD, but had ongoing deterioration in gait and motor functioning on Miglustat, manifested as decreased in ability to perform ADLs and increasingly frequent falls and a tendency to run into things, with resultant constant bruising. She has remained on Miglustat to the present.

Expanded Access Protocol

The protocol was developed to allow access to treatment for 001-01, who was showing relatively rapid disease progression and could not enroll in the phase 1/2a trial. In order to treat her brother, 001-02, at the same time, the expanded access application was submitted to FDA as an intermediate-size patient population IND (IND 119856). The protocol was designed to parallel the ongoing phase 1/2a trial, with 2-week dosing intervals as opposed to the 4-week intervals in the phase 1/2a trial. Several individual expanded access protocols^{21,23} and the NIH phase 1/2a protocol¹⁸ were reviewed and used to develop the protocol described in this study.

The Rush University Medical Center IRB approved the protocol, and legal guardians of all subjects signed informed consent. At age 18, subjects capable of consenting (subject 001-02 and 001-03) resigned consent for themselves. A formulation of HP β CD with a specific chemical fingerprint was obtained from Janssen Research & Development, LLC initially and then Vtesse, Inc. (VTS-270, same formulation) and in all cases was administered by intrathecal infusion via lumbar puncture every two weeks. The initial protocol was written to dose escalate from 200 mg to 400 mg (accepted dose range at the time) over 4 months based on safety. Subsequently, dosing data in the NPC cat¹⁷ suggested that higher doses would likely be optimal when tolerated. The protocol was amended to allow dosing based on tolerability within a range from 200 mg-1200 mg. Actual dosing for the 3 patients is shown in Figure 1.

Numerous safety parameters were monitored (Table 2). Effects on NPC1 disease progression were monitored with neurological exams, clinical data, and objective measures to track neurological function in 5 NPC-affected domains, including 1) cognitive/language, 2) gait/balance, 3) fine motor, 4) swallowing, and 5) eye movements. Global disease severity was followed with the NPC-SS. Specific measures and schedule of testing are shown in Table 2.

Most measures used for cognitive/language and fine motor testing were standardized assessments, including the following: Weschler Intelligence Scale for Children-Fifth Edition (WISC-5)²⁵ and Weschler Adult Intelligence Scale-Fourth Edition (WAIS-4),²⁶ Mullen Scales of Early Learning (MSEL, assessed both cognitive and language ability for 001-01 who could not perform the WISC-5 or CELF-4),²⁷ Clinical Evaluation of Language Fundamentals-Fourth Edition (CELF-4),²⁸ Wide Range Assessment of Memory and Learning-Second Edition (WRAML-2),²⁹ Delis-Kaplan Executive Function System (D-KEFS),³⁰ 9-Hole Pegboard Test (9NPT),³¹ and Purdue Pegboard Test (PPT).³² Other tests are more novel measures and additional description for these is provided below. Data is reported over 24–40 month periods, with the last data point on the charts in the Results section based on the frequency of test administration and when tests were last administered.

NIH Toolbox Cognitive Battery (NIH_TCB)

The NIH-TCB is a repeatable battery of iPad-administered cognitive tests designed to minimize floor/ceiling effects and administration time, validated with normative data for ages 3–89 years from 4500 individuals in the USA.^{33,34} The NIH-TCB consists of 8 subtests, including Dimensional Change Card Sort (cognitive flexibility), Flanker (inhibition and visual attention), Picture Sequence Memory (episodic memory), List Sorting (working memory), Pattern Comprehension (processing speed), Oral Reading Recognition (letter identification and reading), and Picture Vocabulary (receptive vocabulary). The battery was administered as described previously.³⁵

Balance Testing via Computerized Dynamic Posturography (CDP)

Balance testing via CDP was performed using the Neurocom® Smart Balance Master system (NeuroCom International, Inc.)³⁶ as described previously.³⁷ CDP tests include the sensory organization test (SOT, balance under different conditions of altered sensory input), the motor control test (MCT, response latencies to balance perturbations), and the limits of stability test (LOS, postural stability based on excursion of center of mass towards visual targets).

Gait and Functional Mobility Measures

The instrumented Timed Up and Go (i-TUG) was performed by all patients, and the 25-meter 2-minute walk tests (i-WALK) were performed by 001-02 and 001-03 using the commercially available APDM Mobility Lab™ six inertial sensor system (APDM™; Oregon)³⁸ as previously described.³⁹ Five variables aberrant in patients with cerebellar ataxia⁴⁰ were a-priori chosen for analysis: stride velocity, stride velocity variability, percentage of gait cycle in double-limb support, turn duration and turn-to-sit peak velocity. Gait/turn variables were collected from the i-WALK in 001-02 and 001-03. 001-01 could not reliably perform the 2-minute i-WALK, so her gait/turn variables were collected from the i-TUG. The turn-to-sit velocity scores were obtained from the i-TUG for all patients. Age matched normative data for teens/young adults collected by our group were used for comparisons.

Swallowing Function

Swallowing was assessed via videofluoroscopic swallowing study (VFSS) using a standardized protocol with cup sips of barium-containing thin and thickened liquids, pudding and bread. Fluoroscopic images from the VFSS were captured in both the lateral and anterior-posterior planes at 30 frames per second. Recorded swallows were analyzed by video review.

The Modified Barium Swallowing Impairment Scale (MBSImp)⁴¹ and the Penetration-Aspiration Scale (PAS)⁴² were used to objectively score each swallow. The MBSImp is a validated tool used to objectively score 17 different swallowing physiology parameters on a Likert scale (6 oral, 10 pharyngeal, 1 esophageal phase) visible during a VFSS. The individual parameter scores are summed and an overall swallowing impairment score (higher=more impairment) for each swallowing phase is determined.

The Penetration-Aspiration Scale (PAS) is an 8-point ordinal scale with which the clinician rates presence, severity, and patient response to penetration or aspiration; higher scores indicate more impairment. PAS is rated for all swallows, and the worst PAS score observed during the exam is reported.

Videonystagmography

Videonystagmography (VNG) is an eye-movement evaluation that utilizes an infrared eye-tracking system to calculate pupil position and angle of gaze. Measures derived include smooth pursuit (patient follows moving target) and random saccade testing (patient moves eyes rapidly to target of interest), in both the horizontal and vertical planes. Smooth pursuit is scored on eye speed relative to target speed (gain), right/left and up/down asymmetry, and position of the eye relative to target position (phase). Random saccade tests are scored on peak velocity, accuracy, and latency of eye movement. Smooth pursuit gain and random saccade velocity are expected to be sensitive to eye movement abnormalities in NPC and are reported here.

Niemann-Pick Type C Neurological Severity Scale (NSS)

The NSS¹⁹ consists of a rating of clinical signs and symptoms of NPC in nine major and eight minor domains and gives an overall rating (range 0–61) reflecting overall severity of disease. Hearing items were scored at baseline to evaluate disease severity, but efficacy assessment scores excluded hearing and auditory brainstem response items, as hearing loss is a known side effect of HP β CD.^{43,44}

24-Hydroxycholesterol (24(S)-HC) Biomarker

Biochemical target engagement was measured by determination of (1) plasma 24(S)-HC concentrations at pre-dose and 8, 24, 30, 48, and 72 hours post-dose after either saline or HP β CD infusion²⁰ and (2) area under the curve (AUC_{8–72}) relative to the pre-dose 24(S)-HC concentrations for each dose, and the difference between drug response and saline response determined by subtracting the AUC_{8–72} for the saline infusion from the AUC_{8–72} for each dose.

RESULTS

Clinical Status Relative to Pretreatment Baseline

001-01 has shown increased spontaneous language, is reading short sentences, singing and laughing again, and carries out directions faster. In addition, all choking on solid food and episodic vomiting has resolved, with some residual choking on clear liquids. 001-01 showed initial improvement in gait but subsequent worsening of foot dystonia has resulted in return of gait to roughly baseline function. There has been mild high-frequency sensorineural hearing loss treated with hearing aids, which does not impact conversational responses or functioning. There was persistent ataxia and tiredness at 1200 mg (Table 3) and milder post-dose ataxia and tiredness at 900 mg, lasting 3–7 days. On 750 mg these symptoms are mild, last <48 hours post-dose and do not impact functioning.

001-02 has had stable school performance and graduated high school with a regular curriculum and some accommodations. He had mild-to-moderate mid-to-high frequency hearing loss, which incremented at the first dose of 600 mg and above, which is treated with hearing aids and has minimal impact on function and school performance in his current community college program. He had mild post-dose tiredness for several days after each dose of 900 and 1200 mg, but this is minimal, <24 hours post-dose and does not impact functioning since dose reduction to 750 mg (Table 3).

001-03 has had stable performance in a community college and subsequent job training program and does well with office work. Her gait is steadier and her tandem is improved; she is less prone to falling and no longer has bruises from bumping into things. Fine motor and drawing skills are overall improved. She continues on a dose of 300 mg (Table 3) due to an incremental hearing loss and tinnitus with each of three 400 mg doses. She has moderate mid-to-high frequency hearing loss that does not significantly impact daily life or work performance with use of hearing aids. She has not had post-dose tiredness or gait/balance changes.

Adverse Events

Aside from hearing changes and post-dose tiredness/ataxia known to be associated with higher doses of HPβCD, adverse events have been predominantly unrelated to the lumbar punctures (LPs) or HPβCD (Table 3). Post-LP headaches and nausea in 001-01 and 001-02 for several initial doses essentially resolved after switching to the Whitacre needle for LPs.

Longitudinal Performance on Measures of Neurological Function Relative to Baseline

Performance on all measures administered, divided by domain, is shown at baseline and at the most recent determination (3 years of treatment with HPβCD for 001-01 and 001-02 and 2.5 years for 001-03) in supplemental Table 4.

Cognitive/Language/Memory Performance

001-01 has shown variable but improved performance on MSEL subscores since initiating HPβCD (Figure 2a), most notably in expressive language. 001-02 has shown gradual improvement in his WISC-5/WAIS-4 IQ score, CELF-4 Core Language and WRAML-2 General Memory scores (Figure 2b), and his D-KEFS scores are stable to improved. 001-03 has shown gradual improvement in the WAIS-4 IQ score, with stable performance for the CELF-4 Core Language, WRAML-2 General Memory, and D-KEFS scores (Figure 2c). NIH TCB scores have been essentially stable for 001-02 and 001-03 with an increase in the Pattern Comparison Processing Speed subscore in 001-02 (Figure 3a-d).

Balance and Gait Performance

001-01 showed initial improvement on the i-TUG in stride velocity, double support time, and turn duration, but most of these have returned toward baseline (Figure 4a) largely due to increased foot dystonia. 001-02 has had normal or near normal scores on most i-WALK and i-TUG gait measures from the beginning of treatment (Table 4). Despite his normal neurological exam, CDP detected subtle abnormalities in balance on the SOT (Figure 4b), which have improved and are now normal. In general, 001-03 has shown stable or slightly

improved performance on the i-WALK and i-TUG. Stride velocity, double support time, and gait variability all improved slightly (14–20%); remaining variables were unchanged. She has shown dramatic improvement in balance on the SOT (Figure 4b). Scores on the MCT and LOS for both 001-02 and 001-03 have been stable to slightly improved, with some variables reaching the normal range for 001-03 (Table 4).

Fine Motor Performance

001-01 cannot complete these tasks. Mildly subnormal performance on all measures from both the PPT and the 9HPT at baseline for 001-02 has improved toward or into the normal range (Figure 5a,b,d). 001-03 had substantial impairment on both tests at baseline due to her significant intention tremor, but she has shown stable performance on all pegboard scores (Figure 5a,c,e).

Swallowing Function

All three patients have shown substantial improvement in oral and pharyngeal phases of swallowing function as rated by the MBSImp (Table 4; Figure 6) and PAS. The esophageal phase has remained functional since baseline for all three patients.

Patient 001-01 initially showed oral and pharyngeal weakness/incoordination resulting in frequent coughing during meals and aspiration of liquids (PAS=7). Overall coordination, swallowing trigger, hyolaryngeal excursion, and airway protection have improved. She now has occasional laryngeal penetration but no aspiration (PAS=5). Patient 001-02 initially showed mild oropharyngeal weakness/incoordination resulting in trace aspiration of thin liquids (PAS=7). Overall strength has improved with no aspiration (PAS=2). Patient 001-03 initially showed mild-moderate oropharyngeal weakness/incoordination, resulting in pharyngeal residue, nasal regurgitation and aspiration of liquids without spontaneous cough (PAS=8). Strength and coordination have improved with decreased residue and no nasal regurgitation or aspiration (PAS=1).

Quantitative Eye Movements

001-01 cannot complete these tasks. 001-02 and 001-03 both had substantially abnormal vertical saccade velocities and latencies, which cannot be accurately measured due to use of compensatory techniques like blinking. Horizontal average saccade velocities, representing the average of 30 saccades to a target in each measurement, have been essentially stable for both subjects (Table 4). Horizontal pursuit gain has been essentially stable, while vertical pursuit gain has decreased for both subjects.

Global Disease Severity on NSS

NSS score without hearing items has been stable for 001-02 (Figure 7), decreased slightly for 001-03, and initially decreased substantially for 001-01 in the year after starting treatment, with some recent increase predominantly due to emergence of episodes of cataplexy and narcolepsy and worsening of gait back toward baseline.

Biomarker of Target Engagement

The 24(S)-HC AUC₈₋₇₂ for the averaged first two infusions at each dose showed an increase from saline at doses of 500 mg and over for 001-01, all doses for 001-02, and at doses of 400 mg and 300 mg for 001-03 (Figure 8). A dose-response was seen for 001-01 and 001-02. Thus, there was evidence of target engagement at the doses at which all three patients were treated chronically.

DISCUSSION

This study presents 3 patients treated with IT HP β CD through expanded access for 2.5–3 years, all followed with repeated measures in 5 neurological domains highly relevant to the disease course in NPC. Adverse events were either unrelated to drug or were dose-dependent side effects that fell into very specific symptom categories, including moderate mid-high frequency hearing loss with preserved low frequency hearing and post-dose tiredness/ataxia, known effects of treatment with higher doses of HP β CD. Hearing loss and need for hearing aids was a concern; however with the hearing aids, hearing loss does not currently alter the ability of any of these patients to function, suggesting this is a fair trade-off for stabilization of NPC progression, which would have impaired function much more than the hearing loss. In addition, hearing loss would typically appear from NPC anyway, albeit more gradually, as the disease progresses. Finally 001-01 and 001-02 were increased to doses that produced excessive tiredness and had additional hearing loss at those doses before dose reduction. This situation would no longer need to occur due to better understanding of dosing limits and dose-limiting neurological side effects with ongoing experience with HP β CD treatment over the past few years. 001-03 has an unusual sensitivity to hearing loss with HP β CD, as the extent of hearing loss seen in this patient at the 400 mg dose, is not known to have been observed in any other patient worldwide. Finally, the hearing loss side effect does raise some concern about how to best treat and when to start HP β CD treatment for asymptomatic patients and especially young children who are in the process of developing language skills. The potential long-term benefit of early preventative treatment will have to be weighed carefully against this side effect as more data on the benefits of early treatment become available. Otherwise, the drug and biweekly repeated lumbar punctures were well tolerated and do not impact function at doses ultimately utilized.

Overall stable disease to mild improvement was seen over the multiple years of treatment in all three patients based on the clinical picture and global NSS with hearing items excluded. Individual neurological domains in different patients have shown stable disease, mild improvement (cognitive/language, balance/gait and fine motor), substantial improvement (swallowing), or slight worsening (eye movements) of some parameters based on trajectories of multiple repeated objective measures. Although not as sensitive to change, particularly in the minimally affected 001-02, the NSS scores corresponded well with results on objective testing. Based on the expected worsening (increase) in the NSS (without hearing items) of 8 points/3 years¹⁸ and observed decrease in verbal and non-verbal IQ of about 7 and 11 points, respectively, in NPC1 over 3 years,⁴⁵ treatment with HP β CD appears to have altered the natural history of the disease in the reported patients, all of whom showed an increase in measured cognitive function and two of whom showed an increase in IQ of 9 and 7 points.

This result is consistent with the 18-month result from the phase 1/2a open label trial of HPβCD in NPC1,¹⁸ and with the report of disease stabilization based on the NSS for 14 months in a patient treated through another expanded access protocol.²³

The patients presented in this study represent a wide range of disease severity from severely affected (001-01) to minimal disease (001-02). In the NPC1 cat, initiation of treatment prior to symptom onset results in better success than initiation after symptoms emerge.¹⁷ Likewise, HPβCD is likely to be more successful in stalling disease in humans when initiated early in the disease course. Although HPβCD seemed to stall the disease at all levels of affectedness in the patients presented here, it will take many more years to know how long disease stabilization will occur in each neurological domain in each patient. Despite persistent cognitive, language and swallowing improvements, 001-01 showed an initial improvement in gait parameters followed by worsening, which occurred due to toxicity from higher doses (>750) of HPβCD. When the dose was reduced, there was not full recovery to the maximal improvement observed early in treatment, due worsening foot dystonia, suggesting worsening may occur in certain areas despite stabilization or improvement in others. The post-dose side effect of ataxia and unsteadiness can look similar to disease progression, so it is important to identify the optimal dose. The dose at which side effects occurred varied from one patient to another and tolerability in other patients more recently enrolled in this IND and the NIH phase 1/2a trial, has also varied substantially between patients, suggesting dosing of this treatment needs to be individualized.

Some domains seem to be generally more responsive to treatment than others, with cognition/language and swallowing being most responsive in these patients, gait/balance and fine motor intermediately and more variably responsive between patients, and some eye movement measures showing disease progression not seen in other areas. This pattern of response is similar to the pattern of response in different symptom domains in the phase 1/2a study of HPβCD.¹⁸

A number of novel measures were piloted in this study to explore the ability to interrogate disease domains in a long-term treatment study. CDP testing appeared to provide sensitive measures of subtle balance problems and improvements not detectable on neurological exam in 001-02. For subjects with ataxia, the i-TUG and i-WALK provide assessments of gait speed, time in double support, gait variability and turn duration/velocity that are more sensitive measures of ataxia than simple speed measured in a non-instrumented TUG test. Thus, these measures are particularly suited to tracking gait and balance outcomes in NPC treatment studies given the gait ataxia/apraxia in NPC. The NIH-TCB appeared to provide a useful, repeatable index of cognitive function that could be administered in much less time than standardized instruments. This needs to be explored in more patients for longer time to see if the trajectory of subtest scores in the NIH-TCB reflects that seen over time in standardized tests with corresponding cognitive constructs. Patient 001-03 had very low Trailmaking subtest scores on the D-KEFS due to the high motor demand, while executive function scores on the NIH-TCB were better due to the diminished motor demand of pointing to give answers. As such, the NIH-TCB should have value in minimizing motor interference with accurate cognitive testing in NPC and similar disorders. The MBS-Imp as a swallowing rating proved very sensitive to treatment-induced improvement in swallowing.

The penetration-aspiration scale ratings, the historical standard, showed improvement but were not as sensitive to the type of change as the MBSImp. The VNG proved a fast and efficient way of tracking change in eye movements not detectable on exam.

Limitations of this work include the lack of a control group and treatment through an expanded access protocol in which there are likely more confounding changes due to optimizing support and other treatments than would be seen in a clinical trial. However, these expanded access patients had standard-of-care treatment to which the HP β CD treatment was added. Even with optimized standard of care treatment, patients with NPC progress, and at this point treatment has been long enough that it is highly unlikely based on the natural history of NPC1 disease, particularly in the most affected patient, that the observed length of stabilization of disease would be seen without treatment. Even longer follow up will help confirm this result. There may be learning effects on some of the measures, but this is less likely across multiple objective measures and unlikely on measures such as gait and video swallow studies, which involve activities patients are always performing in day-to-day life. For repeated cognitive tests, previous studies have found practice effects when subjects were assessed using the WAIS-3⁴⁶ and WISC-R,⁴⁷ although these studies did not include individuals with neurological disorders and practice effects appear to be lessened in individuals with lower IQ.⁴⁸ Additionally, the greatest practice effect may occur from the first to second assessment,⁴⁹ and subsequently additional gains from repeat administrations are less (unlike ongoing gains seen for 001-02 and 001-03). Even if some practice effects are occurring on cognitive testing in the patients presented here, the data at the very least suggest disease stability. Although all patients were clearly losing skills on Miglustat before starting HP β CD, particularly 001-01 who was regressing with swallowing and alertness, and regression appeared to stop after starting HP β CD, it is impossible to rule out an effect on progression of the Miglustat or a combined effect of Miglustat and HP β CD, which target lipid storage in NPC via different mechanisms.

The treatment protocol described here has been implemented to create a model for long-term tracking of treatment responses relative to natural history in diseases too rare or too slowly progressive for a placebo-controlled trial. While there is currently a sham-controlled phase 2/3 trial evaluating effects of HP β CD (VTS-270) over a year, older patients and those with mild disease are not eligible, as it is expected that the rate of disease progression will be too slow in these patients to detect separation from a control group in a one-year trial, and placebo groups cannot be maintained for multiple years. Models relying on deviation from natural history in a treated cohort are needed for such patients and conditions. N-of-1 and small cohort trials have been proposed for rare diseases, but models are just emerging and are not yet accepted. Data from all outputs from the repeated measures of efficacy in multiple disease-related neurological domains in this protocol can be used to create detailed models for tracking progress over time in each domain. Models can be applied to a larger cohort and extended over longer timeframes to evaluate long-term effects of interventions on disease course for individual patients with NPC and to determine the fraction of patients showing long-term response in each neurological domain. This strategy may serve as a model for assessment of long-term responses to targeted treatment for rare diseases in general.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Diagram of dosing trajectory for the three patients during participation in the expanded access protocol.

Figure 2.

Cognitive and language performance at baseline and over the course of treatment for 001-01 on the Mullen Scales of Early Learning given in age-equivalencies for areas of function (a), on the WISC/WAIS (full scale IQ), CELF (core language), and WRAML (general memory) given as standard scores for the overall composite on each test for 001-02 (b) and 001-03 (c).

Figure 3.

Raw (a,c) and computed (b,d) scores on the NIH-TCB measures for 001-02 (a,b) and 001-03 (c,d) during the course of treatment. NIH-TCB testing was missed at several of the 3 month intervals (33 and 36 months for 001-02 and 27 and 30 months for 001-03) due to problems with the equipment. Subsequent ongoing data collection is occurring.

Figure 4.

Performance over time on motor measures including relevant instrumented gait measures for 001-01 (a) and on the Neurocom SOT (b) for 001-02 and 001-03. SOT scores are a measurement of postural sway under different conditions range from 0 to 100, where 0 represents a fall and higher scores represent less sway. The composite SOT score is calculated as a weighted average of all six conditions.

Figure 5.

Performance over time on the 9-Hole Pegboard task based on speed of performance and number of pegs placed for 001-02 and 001-03 (a) and for number of pegs placed on the Purdue Pegboard Left and Right hands for 001-02 (b) and 001-03 (c), and for both hands and assemblies for 001-02 (d) and 001-03 (e). There was an interruption in testing on the Purdue pegboard from 27–40 weeks for 001-02 and for 21–35 weeks for subject 001-03. When testing was resumed performance was similar to the prior testing result.

Figure 6. Performance on video swallow studies as rated with the MBSimp rating scale for the oral phase (a) and the pharyngeal phase (b) for all three patients. Lower scores represent improvement.

Figure 7. NP-C Neurological Severity Scale (NSS) scores with hearing excluded over the course of treatment for all three subjects.

Figure 8.

HPBCD-specific 24(S)-HC area under the curve (AUC) from 8–72 hours was calculated as the plasma 24(S)-HC AUC for baseline saline infusion subtracted from the plasma 24(S)-HC AUC for each dose. Each plotted point represents the average of AUC8-72 determinations from the first two infusions at each dose.

Table 1

Cohort Characteristics at Entry into the HPβCD Treatment Protocol

Subject	Age/Sex	Weight (kg)	IQ	NSS	Age Onset/Dx	NPC1 Mutations	Clinical Pattern
01-001	14 F	44.9	<20; AE=21 mo	31	6/12	c.410C>T p.Thr137Met c.2000C>T p.Ser667Leu	Cortical cognitive>motor
01-002	15 M	58.4	68	2	13/13	c.410C>T p.Thr137Met c.2000C>T p.Ser667Leu	Cortical cognitive>motor
01-003	17 F	59	79	10	10/16	c.2366G>A p.Arg789His c.3425T>C p.Met1142Thr	Cerebellar motor>cognitive

All subjects were Caucasian. Age of onset refers to appearance of first neurological symptom. All 3 subjects went on Miglustat at same age as diagnosis. The pArg789His mutation was not previously described, but affects a conserved amino acid residue, and filipin staining and cholesterol esterification rate was abnormal consistent with NPC1 diagnosis.

Table 2

Schedule of Assessments Employed in the HPβCD Treatment Protocol

Assessment	Baseline	Subsequent Infusion Visits	Every 12 weeks	Every 6 months
Safety				
Medical or interval history	X	X		
Vital signs with height/weight	X	X		
Physical/neurological exam	X	X		
CBC/serum chemistries/lipid panel	X			X ¹
Urinalysis	X			X ¹
CSF evaluations	X			X ¹
EKG	X			X ²
Audiologic testing	X			X ³
ABR	X			X ⁴
Efficacy				
Cognitive/language domain				
WISC/WAIS	X			X
CELF-4	X			X
WRAML	X			X
D-KEFS	X			X
NIH-TCB	X		X ⁵	
Gait/Balance				
Neurocom	X		X ⁵	
iTUG	X		X ⁵	
Fine Motor				
9-HPT	X		X ⁵	
Purdue Pegboard	X		X ⁵	
Swallowing				
Video Swallow Study	X			X ⁶
Eye Movements	X		X ⁵	
VNG				
Global NSS	X			X
Biomarker				
Plasma 24(S)- hydroxycholesterol efflux	X	X ⁷		

Frequency of assessments depicted in the Table represent the current protocol. Footnotes describe adjustments in assessment frequency which occurred through protocol amendments.

¹These tests were initially prior to every infusion, with CBC and U/A also done at 48 hours after infusions the first 5 months. At 21 months they were decreased to every 3 months, and at 28 months reduced to every 6 months, the current frequency.

²EKG was initially done before and after every infusion for the first 10 infusions and then before every infusion. At 13 months these were reduced to after infusions associated with a dose increase and otherwise every 6 months. At 28 months these were reduced to yearly.

³ Audiologic testing was initially done before each infusion. At 21 months this testing was reduced to monthly until there were 3 stable tests after each dose increase, and then every 3 months. At 28 months testing was reduced to every 6 months after the 3 stable monthly tests following the last dose increase.

⁴ ABR was initially obtained every 6 months but at 13 months decreased to yearly and only required if hearing change since last ABR.

⁵ Gait/balance, fine motor and eye movement testing was initially done every 2 months; at 2 years this testing was decreased to every 3 months.

⁶ Swallow study was initially done every 6 months but at 13 months was decreased to every year.

⁷ Biomarker testing was done pre- and post-infusion as described after the first two infusions for each dose increase. At 2 years this testing was discontinued.

Abbreviations in this table are as follows: CBC=Complete Blood Count, CSF=Cerebrospinal Fluid, EKG=electrocardiogram, ABR=Auditory brainstem response, WISC= Weschler Intelligence Scale for Children, WAIS=Weschler Adult Intelligence Scale, MSEL=Mullen Scales of Early Learning, CELF 4=Clinical Evaluation of Language Fundamentals – Version 4, WRAML= Wide Range Assessment of Memory and Learning, D-KEFS= Delis-Kaplan Executive Function System, iTUG=instrumented Timed Up and Go, 9NPT=9Hole Pegboard Test, VNG=Videonystagmography, NSS=Niemann-Pick type C Neurological Severity Score

Table 3

Adverse Events Observed Over Entire Treatment Period

Events Unrelated to Drug or Lumbar Punctures (# events)				
	Subject	001-01	002-02	001-03
Vomiting		3		
Gastroenteritis		5		
Pneumonia (community acquired)		4		
Bronchitis		2		
Upper Respiratory Infection		5	4	4
Sinus Infection				1
Mouth Abscess (due to wisdom tooth removal)				1
Neutropenia		1		
Menorrhagia				1
Anemia				1
Laceration (due to falls)		2		
Acne			1	
Ringworm				1
Events Related to Lumbar Puncture (# events) *				
Vomiting		1	4	
Headache			4	
Events Related to Drug (Dose at Which Event Occurred)				
High-Frequency Hearing Loss		600	600	400
Mid-Frequency Hearing Loss		900	900	400
Transient Ataxia (24–48 hours)		750		
Transient Lethargy (24–48 hours)		750	750	
Persistent Ataxia (48 hours-2 weeks)		900		
Persistent Lethargy (48 hours-2 weeks)		900	900	

* Only 1 episode of vomiting and headache in 001-02 occurred after switching to the Whitacre