Intrathecal 2-hydroxypropyl-β-cyclodextrin decreases neurological disease progression in Niemann-Pick disease, type C1: a non-randomised, open-label, phase 1–2 trial

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Summary

Background Niemann-Pick disease, type C1 (NPC1) is a lysosomal storage disorder characterised by progressive neurodegeneration. In preclinical testing, 2-hydroxypropyl-β-cyclodextrins (HPβCD) significantly delayed cerebellar Purkinje cell loss, slowed progression of neurological manifestations, and increased lifespan in mouse and cat models of NPC1. The aim of this study was to assess the safety and efficacy of lumbar intrathecal HPβCD.

Methods In this open-label, dose-escalation phase 1–2a study, we gave monthly intrathecal HPβCD to participants with NPC1 with neurological manifestation at the National Institutes of Health (NIH), Bethesda, MD, USA. To explore the potential effect of 2-week dosing, three additional participants were enrolled in a parallel study at Rush University Medical Center (RUMC), Chicago, IL, USA. Participants from the NIH were non-randomly, sequentially assigned in cohorts of three to receive monthly initial intrathecal HPβCD at doses of 50, 200, 300, or 400 mg per month. A fifth cohort of two participants received initial doses of 900 mg. Participants from RUMC initially received 200 or 400 mg every 2 weeks. The dose was escalated based on tolerance or safety data from higher dose cohorts. Serum and CSF 24(S)-hydroxycholesterol (24[S]-HC), which serves as a biomarker of target engagement, and CSF protein biomarkers were evaluated. NPC Neurological Severity Scores (NNSS) were used to compare disease progression in HPβCD-treated participants relative to a historical comparison cohort of 21 NPC1 participants of similar age range.

Findings Between Sept 21, 2013, and Jan 19, 2015, 32 participants with NPC1 were assessed for eligibility at the National Institutes of Health. 18 patients were excluded due to inclusion criteria not met (six patients), declined to participate (three patients), pursued independent expanded access and obtained the drug outside of the study (three patients), enrolled in the RUMC cohort (one patient), or too late for the trial enrolment (five patients). 14 patients were enrolled and sequentially assigned to receive intrathecal HPβCD at a starting dose of 50 mg per month (three patients), 200 mg per month (three patients), 300 mg per month (three patients), 400 mg per month (three patients), or 900 mg per month (two patients). During the first year, two patients had treatment interrupted for one dose, based on grade 1 ototoxicity. All 14 patients were assessed at 12 months. Between 12 and 18 months, one participant had treatment interrupted at 17 months due to hepatocellular carcinoma, one patient had dose interruption for 2 doses based on caregiver hardship and one patient had treatment interrupted for 1 dose for mastoiditis. 11 patients were assessed at 18 months. Between Dec 11, 2013, and June 25, 2014, three participants were assessed for eligibility and enrolled at RUMC, and were assigned to receive intrathecal HPβCD at a starting dose of 200 mg every 2 weeks (two patients), or 400 mg every two weeks (one patient). There were no dropouts in this group and all 3 patients were assessed at 18 months. Biomarker studies were consistent with improved neuronal cholesterol homoeostasis and decreased neuronal pathology. Post-drug plasma 24(S)-HC area under the curve ($AUC_{8\text{-}72}$) values, an indicator of neuronal cholesterol homoeostasis, were significantly higher than post-saline plasma 24(S)-HC $AUC_{8\text{-}72}$ after doses of 900 mg (p=0·0063) and 1200 mg (p=0·0037). CSF 24(S)-HC concentrations in three participants given either 600 or 900 mg of HPβCD were increased about two fold (p=0·0032) after drug administration. No drug-related serious adverse events were observed. Mid-frequency to high-frequency hearing loss, an expected adverse event, was documented in all participants. When managed with hearing aids, this did not have an appreciable effect on daily communication. The NNSS for the 14 participants treated monthly increased at a rate of 1·22, SEM 0·34 points per year compared with 2·92, SEM 0·27 points per year (p=0·0002) for the 21 patient comparison group. Decreased progression was observed for NNSS domains of ambulation (p=0·0622), cognition (p=0·0040) and speech (p=0·0423).

Interpretation Patients with NPC1 treated with intrathecal HPβCD had slowed disease progression with an acceptable safety profile. These data support the initiation of a multinational, randomised, controlled trial of intrathecal HPβCD.

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Introduction

Niemann-Pick disease, type C (NPC) is a recessive, lysosomal storage disorder characterised by endolysosomal accumulation of unesterified cholesterol.[1] NPC results from mutation of either *NPC1* or *NPC2*, with most cases due to impaired NPC1 function.[2] The estimated prevalence of classic NPC disease is about 1 in 100 000.[1] The NPC1 disease phenotype is heterogeneous with respect to both age of onset and clinical presentation.[1,3–6] Systemic manifestations such as hepatosplenomegaly, neonatal cholestatic jaundice, or splenomegaly can lead to diagnosis; however, NPC1 is frequently not diagnosed until after the onset of neurological symptoms. Onset of neurological disease is insidious and often presents as clumsiness or learning difficulty in school. Onset is usually in childhood, although recognition of adult-onset disease is becoming more frequent.[1] Cerebellar ataxia and cognitive impairment progress over years with death generally 10–15 years after onset. Other neurological symptoms can include vertical supranuclear gaze palsy (VSGP), gelastic cataplexy, seizures, and mid-to-high-frequency hearing loss. Although often not recognised, VSGP is typically the first neurological symptom and, along with gelastic cataplexy, is indicative of NPC1 in children. Adult onset NPC1 frequently presents with psychiatric disease. NPC1 disease progression has been characterised with the NPC Neurological Severity Score (NNSS), a Likert-like scale that assesses severity of clinically relevant signs and symptoms in nine major domains and eight minor domains (appendix p 10).[5–7] No therapies for NPC1 disease have been approved by the US Food and Drug Administration (FDA). Miglustat has been approved by the European Medicines Association (EMA) and other regulatory agencies based on a controlled trial and long-term extension studies;[8–10] however, there remains an unmet medical need for therapies that more effectively slow the neurological progression of NPC1 disease.

The potential therapeutic efficacy of 2-hydroxypropyl-β-cyclodextrins (HPβCD) was discovered serendipitously when it was used as an excipient to administer allopregnanolone in NPC1 mice.[11] Subsequent studies, however, suggested that HPβCD, rather than the neurosteroid, was the active moiety.[12,13] Translation of this potential therapy to children with NPC1 is supported by several studies in both mice[12–14] and cats[15] that show a marked delay in progression of neurological signs and

Research in context

Evidence before this study

We searched PubMed for relevant studies of therapies for Niemann-Pick Disease, type C1 published between database inception and March 7, 2017. Search terms included either "Niemann-Pick Disease" or "NPC1" combined with "therapy" or "cyclodextrin". We also searched ClinicalTrials.gov using the search term "Niemann-Pick." Studies that focused on Niemann-Pick Disease, type A or type B (sphingomyelinase deficiency) were excluded. We did not apply any language restrictions. Miglustat has been approved for the treatment of Niemann-Pick disease, type C1 (NPC1) by the European Medicines Agency and other regulatory agencies but not the US Food and Drug Administration. There are no other approved treatments for NPC1 and no approved therapy in the United States. Multiple preclinical studies in mouse and cat models of NPC1 provide a rationale to investigate the safety and efficacy of intrathecal 2-hydroxypropyl-β-cyclodextrin (HPβCD) in the treatment of neurological manifestations of NPC1. These preclinical studies showed both reduction in neurological signs and extended lifespan in treated animals. A number of anecdotal case reports describing intravenous or intrathecal use of HPβCD have been published. With respect to trials of HPβCD in NPC1, ClinicalTrials.gov only lists this phase 1–2a trial (NCT01747135), our ongoing phase 2b/3 intrathecal trial (NCT02534844), and two intravenous trials of a different HPβCD preparation (NCT02939547 and NCT02912793).

Added value of this study

An effective therapy to slow the progression of neurological signs and symptoms of Niemann-Pick disease, type C1 is a critical unmet medical need. In this study we provide a comparison of neurological disease progression in a cohort of NPC1 participants treated with intrathecal HPβCD and a control cohort of NPC1 patients followed in a Natural History study. This study provides information on safety of intrathecal HPβCD therapy and indicates a decreased rate of neurological disease progression in the treated cohort. Measurement of biomarkers provided additional support for improved neuronal cholesterol homoeostasis and decreased neuronal damage.

Implications of all the available evidence

The biomarker, safety, and clinical efficacy data reported here demonstrates an acceptable safety profile, pharmacodynamic evidence of improved neuronal cholesterol homoeostasis, biomarker data suggestive of decreased neuronal damage, and decreased neurological progression in HPβCD-treated participants. This study provides the rationale to proceed to a phase 2b–3 study. Data from a multicentre, international, randomised, sham-controlled phase 2b–3 study is needed to confirm the results of this study and obtain FDA and EMA approval.

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See Online for appendix

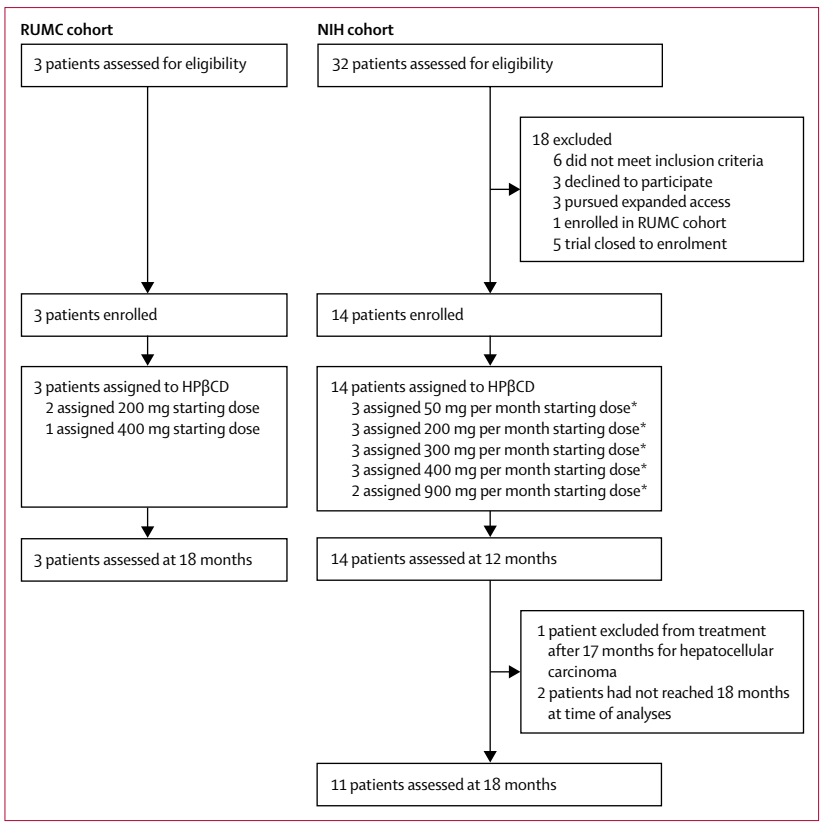

Figure 1: **Trial profile**
RUMC=Rush University Medical Center. *Dose was advanced based on tolerance and safety data from higher dose cohorts. NIH=National Institutes of Health. HPβCD=2-hydroxypropyl-β-cyclodextrins.

death. We aim to establish safety and potential efficacy of escalating doses of lumbar intrathecal HPβCD in patients with NPC1.

Methods

Study design

We performed an open-label, dose-escalation study to assess safety, pharmacodynamics, and efficacy of monthly intrathecal doses of 50–1200 mg of a well characterised HPβCD mixture with a specific compositional fingerprint and limits for impurities (appendix p 3, VTS-270; Vtesse, Gaithersburg, MD). HPβCD was formulated as a 20% solution and diluted in saline to provide a volume of 10 mL, which was infused over 2–3 min into the lumbar intrathecal space by a licensed independent practitioner. Dosing details are provided in figures 1, 2, and the appendix (p 2). The study was approved by applicable Institutional Review Boards. Both the phase 1–2a trial of HPβCD (13-CH-0001) and the NPC1 NIH historical trial (06-CH-0186) were approved by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Institutional Review Board. The Rush University Medical Center Institutional Review Board approved the aspects of the study related to the three RUMC participants.

Participants

In this open-label, dose-escalation phase 1–2a study, we assessed safety and clinical efficacy of intrathecal HPβCD. Eligible patients had NPC1 with neurological manifestations, were aged 2–25 years, weighed more than 12 kg, were willing to discontinue nonprescription supplements, and willing to participate in all aspects of the trial. Patients were excluded if they had severe neurological manifestations of NPC1. All participants were recruited from the National Institutes of Health, Bethesda, MD, USA. A comparison cohort of patients with NPC1 disease with longitudinal assessments was derived from the National Institutes of Health Natural History study (NHx; appendix pp 2, 11). To explore the potential effect of 2-week dosing, additional participants were enrolled with the same criteria in a parallel study at Rush University Medical Center (RUMC; Chicago, IL, USA; appendix pp 2–3). The diagnosis of NPC1 disease was established by a combination of clinical, cellular, and molecular criteria (appendix p 3). Written informed consent was obtained from patients, parents, or guardians.

Assignment and procedures

NIH Patients were non-randomly, sequentially assigned in cohorts of three to receive starting doses of 50, 200, 300, 400, or 900 mg intrathecal HPβCD (figure 1). The dose was advanced based on tolerance and safety data from higher dose cohorts (figure 2). Audiological assessments were obtained monthly before each infusion. Clinical efficacy was assessed with the NNSS.[6] A detailed description of the NNSS (appendix p 10) and baseline individual NNSS component scores (appendix p 4) are provided. NNSS was obtained at baseline and then every 6 months.

NNSS assessments were at 18 months for participants CDA101 and CDA103-111. The 18-month assessment for CDA112 was obtained at 19 months. NNSS data corresponding to CDA102, CDA113 and CDA114 were obtained at 12 months and data corresponding to the three RUMC participants were obtained at 18 months.

Outcomes

Primary outcome was change in 24(S)-hydroxycholesterol (24[S]-HC) $AUC_{8\text{-}72}$ response to drug administration compared with the response after saline administration.[16] Clinical efficacy, as ascertained by the NNSS,[6] was a secondary objective. Pharmacokinetic data will be reported separately.

Plasma 24(S)-HC concentrations were established at pre-dose, 8, 24, 30, 48, and 72 h post-dose after either saline or HPβCD infusion and the area under the curve was established ($AUC_{8\text{-}72}$). Concentrations of fatty acid binding protein 3 (FABP3) and calbindin D in CSF were assayed by Myriad Rules Based Medicine (Austin, TX).

Severity of adverse events was graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03.

NIH cohort

	Subject	Baseline	IT 1	IT 2	IT 3	IT 4	IT 5	IT 6	IT 7	IT 8	IT 9	IT 10	IT 11	IT 12	IT 13	IT 14	IT 15	IT 16	IT 17	IT 18
Cohort 1	CDA101	Saline	50 mg	200 mg	200 mg	200 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	600 mg	600 mg	600 mg	900 mg	900 mg
	CDA102	Saline	50 mg	50 mg	200 mg	200 mg	200 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	600 mg	600 mg	400 mg	DI-2
	CDA103	Saline	50 mg	200 mg	200 mg	200 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	600 mg	600 mg	900 mg	900 mg	900 mg
Cohort 2	CDA104	Saline	200 mg	200 mg	200 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	600 mg	600 mg	600 mg	900 mg	900 mg	600 mg
	CDA105	Saline	200 mg	200 mg	200 mg	200 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	600 mg	DI-3	DI-3	600 mg	600 mg	600 mg
	CDA106	Saline	200 mg	200 mg	200 mg	200 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	600 mg	600 mg	600 mg	900 mg	900 mg	900 mg
Cohort 3	CDA107	Saline	300 mg	DI-1	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	300 mg	300 mg	300 mg	400 mg	400 mg	400 mg
	CDA108	Saline	300 mg	DI-1	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	300 mg	300 mg	300 mg	400 mg	400 mg	400 mg
	CDA109	Saline	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	400 mg	400 mg	300 mg	400 mg	400 mg	400 mg
Cohort 4	CDA110	Saline	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg
	CDA111	Saline	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg	DI-4
	CDA112	Saline	360 mg*	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	1200 mg	900 mg	1200 mg	1200 mg	1200 mg	1200 mg
Cohort 5	CDA113	Saline	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg						
	CDA114	Saline	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg						

RUMC cohort

	Subject	Baseline	IT 1	IT 2	IT 3	IT 4	IT 5	IT 6	IT 7	IT 8	IT 9	IT 10	IT 11	IT 12	IT 13	IT 14	IT 15	IT 16	IT 17	IT 18
Cohort 1	001-01	Saline	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	300 mg	300 mg	300 mg	300 mg	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg
	001-02	Saline	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	300 mg	300 mg	300 mg	300 mg	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg
	001-03	Saline	400 mg	400 mg	DI-1	200 mg	300 mg	300 mg	400 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg

	IT 19	IT 20	IT 21	IT 22	IT 23	IT 24	IT 25	IT 26	IT 27	IT 28	IT 29	IT 30	IT 31	IT 32	IT 33	IT 34	IT 35	IT 36	IT 37
Cohort 1 (continued)	400 mg	400 mg	500 mg	500 mg	500 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	750 mg	750 mg	750 mg	750 mg	750 mg
	500 mg	500 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	750 mg	750 mg	750 mg
	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg

	IT 38	IT 39
Cohort 1 (continued)	750 mg	750 mg
	750 mg	750 mg
	300 mg	300 mg

Figure 2: **HPBCD dosing for NIH and RUMC participants**
DI-1=Dose interruption for ototoxicity. DI-2= Dose interruption for hepatocellular carcinoma. DI-3= Dose interruption for caretaker hardship. DI-4= Dose interruption for mastoiditis. NIH=National Institutes of Health. RUMC=Rush University Medical Center. *Dosing error.

Statistical analysis

Demographic data corresponding to the HPβCD cohort and the NIH historical cohort were compared with independent sample two-tailed *t*-tests for continuous variables or Fisher's exact test for categorical data. Paired two-tailed *t*-tests were used to assess changes in 24(S)-HC, FABP3 and calbindin D concentrations. Spearman statistics were used to assess the audiological data correlations. Fisher's exact test was used for the responder analysis. A nominal p value of 0·05 was considered significant.

No formal calculation of sample size was made for ad-hoc analysis of the NNSS, and given the small sample size we are not estimating confidence intervals. We used a post-hoc mixed model repeated measures approach to assess the efficacy of HPβCD in this population. The NIH historical population was used as the comparison group, and participants were selected based on two criteria: the presence of two or more assessments within a 25-month time period and an age range of 4–24 years at the first of any two or more assessments (to match the established population in the intervention group, whose age ranged from 4·2–23·5 years). The primary analysis estimates the slope as change in score per year from a mixed model repeated measures (MMRM) model with time, group (HPβCD-treated participants or NIH historical study participants), and a group by time interaction term. This approach was selected due to the small sample size and the uneven follow-up in the NIH historical population, making it difficult to include time as a class variable. An unstructured covariance structure is used for fitting each model, due to the stability of the models under this assumption. We estimated the average annual change or annualised slope for each group from the model. We assessed the null hypothesis that the slope in the HPβCD-treated group is equal to the slope in the NIH historical group based on the p value associated with the interaction term in the mixed model.

For the responder analysis, we used a change from baseline to assess the efficacy of HPβCD in individual participants. The NIH historical population was used as

	Control cohort (n=21)	HPβCD treated cohort (n=14)	p value
Age at baseline, years			
Mean (SEM)	10·7 (6·0)	15·1 (5·5)	0·61
Median (range)	10·0 (4·0–21·9)	14·6 (4·2–23·5)	..
Sex			
Male	9 (43%)	7 (50%)	0·73
Female	12 (57%)	7 (50%)	..
Total NNSS at baseline, points			
Mean (SEM)	14·5 (9·7)	19·3 (7·5)	0·72
Median (range)	14 (1–35)	19 (5–32)	..
Total NNSS-hearing at baseline, points			
Mean (SEM)	13·2 (9·4)	17·0 (7·4)	0·77
Median (range)	12 (1–33)	16 (5–32)	..
Age of first NPC symptom, years			
Mean (SEM)	2·3 (3·7)	3·5 (4·3)	0·83
Median (range)	0·6 (0·0–13·0)	1·0 (0·0–12·0)	..
Age of first neurological symptom, years			
Mean (SEM)	5·4 (4·2)	5·9 (3·5)	0·93
Median (range)	3·5 (1·2–15·0)	6·0 (1·0–12)	..
Age of diagnosis, years			
Mean (SEM)	7·1 (6·5)	9·1 (5·6)	0·83
Median (range)	7·0 (0·3–21·0)	9·0 (2·0–20·0)	..
Miglustat use, n (%)			
Yes	16 (76%)	12 (86%)	0·68
No	5 (24%)	2 (14%)	..

NIH=National Institutes for Health. HPβCD=2-hydroxypropyl-β-cyclodextrins. SEM=standard error of the mean.

***Table*: NIH participant demographics and clinical characteristics**

the comparison group; the patient selection criteria were as described for the MMRM approach. For each domain in the NNSS, the value at baseline was subtracted from the value of the same domain during the assessment at the furthest timepoint within the time period. The numerical difference is a direct estimate of improvement of disease in the specific domain (decline in the score), stability of the disease in the domain (no change in score) or worsening of disease in the domain (increase in score). SAS 9.4 was used for statistical analysis of the NPC1 NNSS data and responder analysis. GraphPad Prism was used for other statistical analysis and to generate the figures.

Role of the funding source

The funders had no role in study design, data collection, data analysis, or decision to submit for publication. Janssen Research & Development, a Johnson and Johnson company provided the study drug and both Janssen Research & Development and Johnson and Johnson provided pro-bono preclinical development support. Vtesse supported statistical analysis by Statistics Collaborative. FDP had full access to the data and final responsibility for the decision to submit for publication.

Results

Between Sept 21, 2013, and Jan 19, 2015, 32 patients with NPC1 were assessed for eligibility at the National Institutes of Health. 18 patients were excluded due to not meeting inclusion criteria (six patients), declining to participate (three patients), pursuing expanded access (ie, elected to get the drug via FDA expanded access programme rather than through trial; three patients), enrolling in the RUMC cohort (one patient), and being too late for the trial enrolment (five patients). 14 patients were enrolled and assigned to receive intrathecal HPβCD at a starting dose of 50 mg per month (three patients), 200 mg per month (three patients), 300 mg per month (three patients), 400 mg per month (three patients), or 900 mg per month (two patients). The dose was advanced based on tolerance and safety data from higher dose cohorts (figure 2). Patients initially dosed at 900 mg were maintained at 900 mg for 12 months. Two patients had interrupted treatment for one dose, based on grade 1 ototoxicity. All 14 patients were assessed at 12 months. One patient had treatment interrupted at 17 months due to hepatocellular carcinoma and was excluded from the analysis at 18 months. Between 12 months and 18 months, one patient had treatment interruption for 2 doses based on caregiver hardship and one patient had treatment interrupted for 1 dose for mastoiditis. 11 patients were assessed at 18 months. Between Dec 11, 2013, and June 25, 2014, three participants were assessed for eligibility and enrolled at RUMC, and were assigned to receive lumbar intrathecal HPβCD at a starting dose of 200 mg every 2 weeks (two patients), or 400 mg every 2 weeks (one patient). The dose was advanced based on tolerance (figure 2). There were no dropouts in this group and all three patients were assessed at 18 months. 21 patients with similar patient characteristics to those in this study were identified from the historical database. Participant demographics and baseline clinical characteristics, participation flow, and dosing information are provided in the table, figure 1, figure 2, and appendix (pp 4–5). Mean dose was 289 mg (SEM 68) at 12 months and 423 mg (142) at 18 months for the group treated monthly, except for two patients who were given 900 mg for 12 months (figure 3). Mean dose at 18 months in the patients treated every 2 weeks ranged from 297–481 mg (figure 3).

In preclinical studies, treatment with HPβCD was shown to redistribute lysosomal cholesterol, resulting in modulation of a range of CNS sterol homoeostatic responses, including synthesis of 24(S)-HC.[16] Since 24(S)-HC is derived almost exclusively from neurons in the CNS,[17] measurement of 24(S)-HC in response to HPβCD provides a pharmacodynamic marker of improved neuronal cholesterol homoeostasis. Therefore, the drug response was monitored by measuring plasma 24(S)-HC $AUC_{8\text{-}72}$. 121 of 155 post-drug plasma 24(S)-HC $AUC_{8\text{-}72}$ values were greater than post-saline values; however, plasma responses were more variable and less robust compared with what was observed in preclinical

testing (appendix pp 12–13). Despite the variability, the data suggested a trend for increased 24(S)-HC response at higher doses and significant increases in individual patient responses were observed at 900 mg and 1200 mg (figures 4A and 4B). We also examined CSF 24(S)-HC concentrations before and after HPβCD administration. The CSF 24(S)-HC concentrations in three participants given 600–900 mg of HPβCD were approximately doubled 72 h after drug administration (p=0·0032; figure 4C). These data provide pharmacodynamic evidence of a significant response to HPβCD administration and improved neuronal cholesterol homoeostasis.

Previous work reported increased CSF concentrations of fatty acid binding protein 3 (FABP3)[18] and calbindin D[19] in NPC1. Elevated FABP3 has been reported as a biomarker for neurodegenerative disorders,[20,21] and elevated calbindin D concentrations have been reported in cerebellar injury.[22] Baseline CSF FABP3 concentrations were significantly higher (15·67 ng/mL, SEM 3·38) than published control concentrations (2·36 ng/mL, 0·72; p=0·0016),[18] and last mean treated values decreased significantly compared with baseline (figure 4D; 8·56 ng/mL, SEM 1·36; p=0·0109). Serial values are shown in the appendix (pp 12–13) and eight (57%) of 14 participants treated monthly had a significant negative linear regression slope, whereas no participants had a significant increase in FABP3 (figure 4F). Baseline CSF calbindin D concentrations (532 ng/mL, SEM 69) were significantly higher than control values (0·76 ng/mL, SEM 0·34; p=0·0001),[19] and mean last treated values decreased significantly compared with baseline (figure 4E; 385 ng/mL SEM 56; p=0·0040). Nine (64%) of 14 participants had a significant negative linear regression slope and only one patient had a significant increase (figure 4F and appendix pp 12–13). These data provide evidence that treatment with HPβCD shifts CSF biomarkers of CNS pathology toward normal concentrations.

No serious adverse drug reactions were observed and adverse events are tabulated in the appendix (p 6). Notable expected adverse events included participants with post-lumbar puncture headache (nine [64%] of 14 patients) and ototoxicity (14 [100%] of 14 patients). Notable unexpected adverse events included post-administration unsteadiness and fatigue at doses above 600 mg. This was transient and typically occurred 24–72 h after dosing. The degree of impairment varied between participants, but classified as clinically significant in three (33%) of nine participants at 600 mg, six (50%) of 12 patients at 900 mg, and nine (100%) of nine participants at 1200 mg. The unsteadiness and fatigue might variably attenuate with repetitive dosing at a given dose. One participant presented with hepatocellular carcinoma during the trial. Hepatocellular carcinoma is a rare complication of NPC1,[23–26] and retrospective testing revealed an increased serum concentration of α-fetoprotein at baseline.

Ototoxicity following treatment with HPβCD, probably due to outer hair cell loss,[27] was observed in preclinical testing.[27,28] Progressive mid-to-high-frequency hearing loss is common in NPC1 disease;[29,30] however, additional hearing impairment in participants with NPC1 was associated in this study with administration of HPβCD.

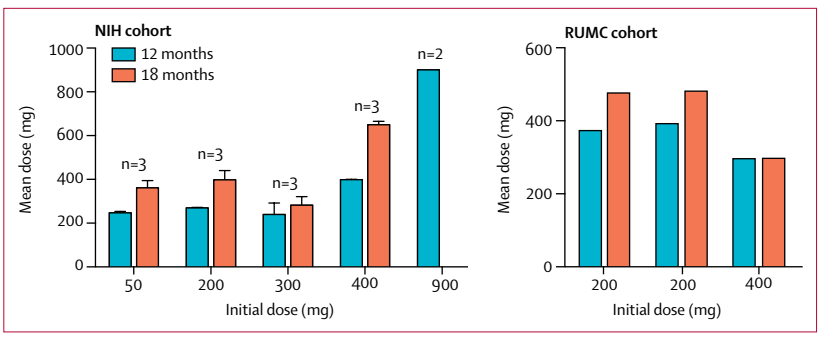

***Figure 3*: Mean doses and SEM of HPβCD at 12 and 18 months by cohort and initial dose**
HPβCD=2-hydroxypropyl-β-cyclodextrins. NIH=National Institutes of Health. RUMC=Rush University Medical Center. HPβCD dose for the NIH cohorts and RUMC participants at 12 months (blue bars) and 18 months (red bars). NIH participants were enrolled in 5 cohorts with escalating initial doses.

Behavioural thresholds for pure-tone stimulation could be established for 12 of 14 participants. Baseline audiograms are shown in figure 5A and last-study audiograms are shown in figure 5B. Hearing loss (>15 dB HL for at least one frequency) was present at baseline in all participants. Based on these audiograms, seven participants were candidates for receipt of hearing aids. After HPβCD administration, all participants had additional mid-frequency to high-frequency hearing loss, and all participants were hearing aid candidates. Change in hearing by frequency is shown in figure 5C. Broad variation in the degree of ototoxicity in individual participants was observed. High-frequency (4/6/8 kHz pure-tone average) hearing loss did not correlate with either mean HPβCD dose (p=0·86, Spearman's correlation coefficient [*r*]=–0·06) or total HPβCD exposure (p=0·64, *r*=–0·15). In contrast, there was a significant negative correlation (p<0·0001, *r*=–0·91) between change in hearing and the degree of high-frequency hearing loss at baseline (figure 5D). These data suggest that there is greater HPβCD ototoxicity in individuals who have not yet lost hearing due to NPC1 disease itself. One RUMC participant had marked sensitivity to HPβCD with CTCAE grade 3 hearing loss upon initial dosing at 400 mg; however, subsequent administration of 300 mg HPβCD every 2 weeks did not result in additional ototoxicity. Although not every patient could reliably self-report tinnitus, it appeared to be associated with HPβCD administration. Tinnitus was limited to the post-dose time period in two patients, but persistent in four of 14 participants.

Clinical efficacy was ascertained by comparing NNSS progression in the 14 NIH HPβCD-treated participants to that observed in a historical cohort of 21 participants of similar age range (table, appendix p 11) followed in an historical NIH study. On average, control patients were younger and had lower NNSS at baseline, but these differences were not significant. The total NNSS for the

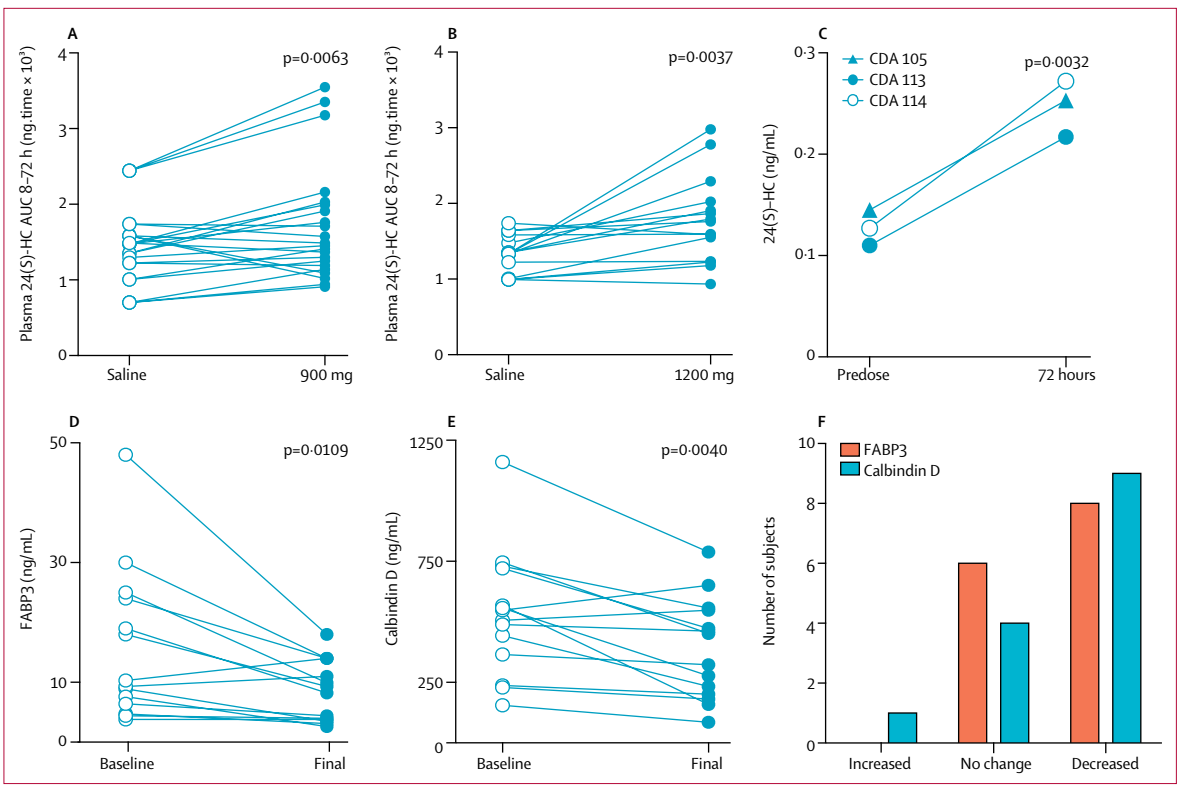

***Figure 4*: 24(S)-HC AUC_{8-72} and cerebrospinal fluid biomarker responses**
24(S)-HC AUC_{8-72}=24(S)-hydroxycholesterol area under the curve. HPβCD=2-hydroxypropyl-β-cyclodextrins. CSF=cerebrospinal fluid. FABP3=fatty acid binding protein 3. 24(S)-HC AUC_{8-72} values increased after intrathecal doses of (A) 900 mg or (B) 1200 mg of HPβCD relative to the values observed after intrathecal infusion of saline. Each paired set of pre and post values represents an individual dose: 18 doses among 8 participants for 900 mg and 13 doses among 7 participants for 1200 mg. (C) CSF 24(S)-HC concentration measured before and 72 h after drug administration in three participants. Significant decreases were observed when comparing baseline and final (D) CSF FABP3 and (E) CSF calbindin D concentrations. (F) Histogram plot of the distribution of individual participant CSF FABP3 and calbindin D responses to monthly HPβCD.

14 participants treated monthly increased at a slower rate of 1·22 points per year (SEM 0·34) compared with 2·92 points per year (SEM 0·27, p=0·0002) for the comparison cohort (figure 6A). The NNSS includes components related to hearing. When the hearing related components were removed, HPβCD-treated participants showed a progression rate of 0·69 points per year (SEM 0·34) versus 2·67 points per year (0·27, p<0·0001) for the comparison group. These data show a significant reduction in disease progression in the HPβCD-treated cohort.

The change in the annualised slope for individual major NNSS subdomains is shown in figure 6B and appendix (p 7). By comparison with the controls, the HPβCD cohort had significantly decreased progression in cognition (p=0·0040) and speech domains (p=0·0423). The ambulation domain was also decreased (p=0·0622). Only the hearing domain had a notable increase (p=0·0518). Heat maps showing individual participant changes for each NNSS major domain are provided for the comparison and HPβCD-treated cohorts (appendix pp 14–15). Individual pre and post-NNSS for eight participants for whom pretrial data were available are provided in the appendix (pp 16–17). Stabilisation or slowing of NPC1 disease progression was seen in six (75%) of these eight participants.

Sensitivity analysis was performed to assess the effect of miglustat therapy. The total NNSS for the 12 participants treated monthly increased at a slower rate of 0·87 points per year (SEM 0·33) compared with 3·10 (SEM 0·27) for the 16 participants in the comparison group (p<0·0001). Significantly decreased progression was seen for the ambulation (p=0·0223), cognition (p=0·0061), and speech (p=0·0218) subdomains (appendix p 8). When the three RUMC participants (treated every 2 weeks) were included in the annualised progression slope, total NNSS decreased from 1·22 to 1·02 and NNSS minus hearing decreased from 0·69 to 0·28 points per year, (appendix p 9). Significantly decreased progression was observed for ambulation (p=0·0117), cognition (p=0·0017), and speech (p=0·0147). A non-significant decrease in progression was reported for memory (p=0·0729).

In a secondary responder analysis, participants in the HPβCD and comparison cohorts were classified as responders if their NNSS minus hearing was stable or improved. In the comparison cohort, 21 (100%) of

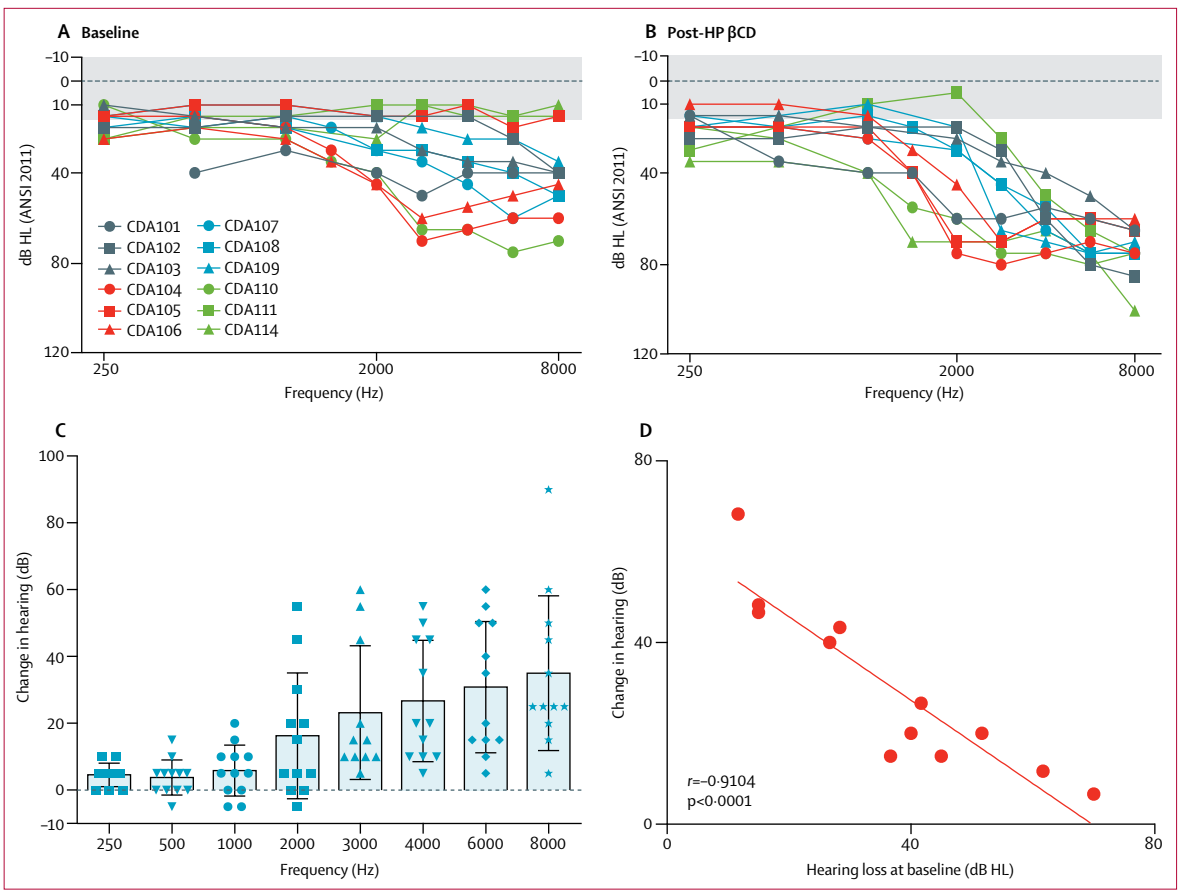

Figure 5: **Characterisation of audiological effects of intrathecal HPβCD**
HPβCD=2-hydroxypropyl-β-cyclodextrins HL=hearing loss. Behavioural audiograms recorded at (A) pre-study and (B) final visit. Behavioural audiograms could not be obtained on two participants due to inability of these participants to do this testing. Data shown are from the most affected ear. The grey region denotes the range of normal hearing sensitivity.[31] (C) Change in hearing from pre-study to last-study assessment plotted by frequency (mean and SEM). (D) Pre-study to last-study hearing change associated with the level of pre-existing hearing loss at baseline for 4/6/8 kHz pure-tone average. r is the Spearman corrlation coefficient.

21 patients had disease progression (figure 6C), whereas seven (50%) of the 14 participants in the HPβCD-treated group had disease progression (figure 6D). The RUMC participants treated every 2 weeks were all responders.

Discussion

In this trial of intrathecal HPβCD we found both biomarker and clinical evidence of efficacy in patients with NPC1 disease. From a safety standpoint, doses up to 1200 mg were generally well tolerated. The transient post-dose ataxia and fatigue observed in this study could be a dose-limiting side-effect, especially if the dose or frequency of dosing is increased. The aetiological basis of this side-effect is not known. Ototoxicity was an expected adverse event based on preclinical work.[27,28] Progressive mid-frequency to high-frequency hearing impairment is common in NPC1 patients[29,30] and seven of 17 participants enrolled in this study had functional deficits in hearing at baseline. At study end, all participants had functional deficits in hearing, but these deficits did not appreciably affect daily communication when managed with hearing aids. The degree of hearing loss was inversely associated with individual participant's baseline hearing. Additional work is required to establish if ototoxicity can be separated from neurological efficacy; however, in the context of a lethal neurodegenerative disorder, the risk of functional hearing impairment that can be managed with hearing aids can be justified.

Our biomarker data support efficacy of HPβCD. In general, the plasma 24(S)-HC response was not as robust as observed in preclinical models.[16] Nonetheless, plasma 24(S)-HC $AUC_{8\text{-}72}$ concentrations increased above that observed in response to intrathecal saline administration at HPβCD doses of 900 mg and 1200 mg. By contrast, the increase in CSF 24(S)-HC concentration after HPβCD administration was unambiguous. These data provide pharmacodynamic support for mobilisation of stored cholesterol in CNS neurons in response to treatment with HPβCD. We also observed that CSF calbindin D and FABP3 concentrations, biomarkers of neuronal damage, decreased significantly in most HPβCD-treated participants. Neither calbindin D nor

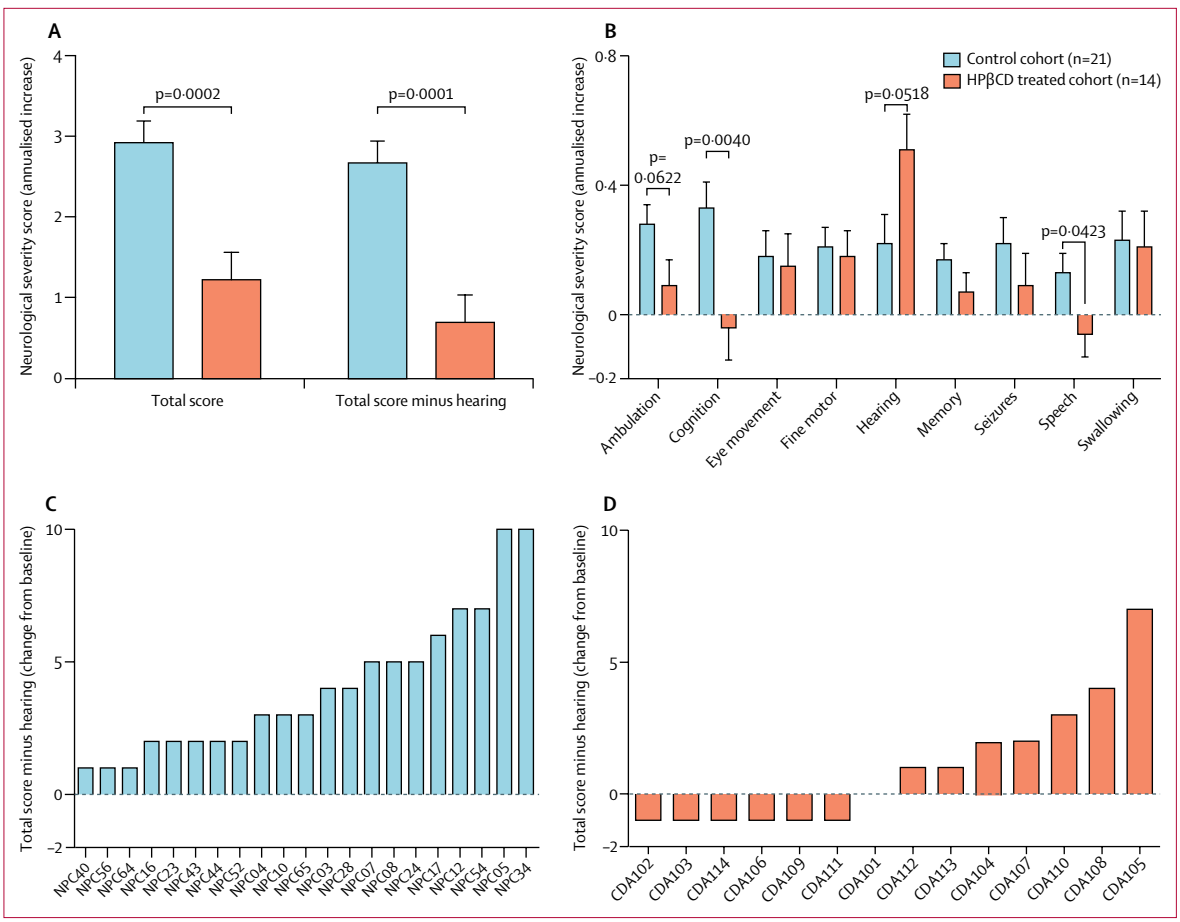

Figure 6: **Clinical efficacy of intrathecal HPβCD**

NNSS=NPC Neurological Severity Score. NPC1=Niemann-Pick disease, type C1. HPβCD=2-hydroxypropyl-β-cyclodextrins.NNSS was used to characterise NPC1 disease progression in 21 control patients (blue bars) and 14 HPβCD-treated participants (red bars). (A) Annualised rate of disease progression, as ascertained by the total NNSS and total NNSS minus hearing components, in HPβCD-treated participants compared with the control patients. Data are from the 12-month assessment for three patients and from the 18-month assessment for 11 patients. (B) Assessment of the individual major components of the NNSS. Annualised rate of disease progression decreased for ambulation, cognition, and speech in the intrathecal HPβCD-treated participants by comparison with the control group. Only the hearing subdomain showed a notable annualised increase in progression in the HPβCD-treated group, which is consistent with the known ototoxicity of HPβCD. Responder analysis was done based on the change from baseline in the NNSS in (C) control patients and (D) HPβCD-treated patients. Individuals with a decreased or stable NNSS minus hearing were considered to be responders. Disease progression was observed in 21 of 21 control patients, whereas only seven of 14 HPβCD-treated participants showed disease progression (p=0·0005).

FABP3 have been established as clinical surrogates, but our observation that CSF concentrations decrease in temporal relationship with HPβCD therapy is consistent with the conclusion that intrathecal HPβCD might decrease neuronal damage in participants with NPC1.

In this study we explored monthly intrathecal doses between 50 and 1200 mg. Scaling based on brain size from cats to human beings would suggest increased efficacy with higher and more frequent doses (ie, every 2 weeks).[15] The data available from the RUMC participants suggests that every 2-week dosing might be more efficacious than monthly dosing. Although higher and more frequent dosing might prove to be more efficacious, ultimately this will be a balance between efficacy and tolerability of the side-effects. Because patient numbers are small in this rare disease, we are exploring higher and more frequent dosing in the context of a placebo-controlled phase 2b–3 trial (data not yet available).

This study has several limitations. First, it relies on a historical comparison group, and is not a randomised, placebo-controlled trial. Second, the clinical efficacy data is based upon an ad-hoc analysis. Third, the dose escalation design focused on establishing safety and tolerability limits our ability to establish dose-response associations with biomarker and clinical data. Nonetheless, the results presented in this report provide compelling evidence that intrathecal HPβCD therapy might decrease neurological disease progression significantly in NPC1 patients. Specifically, we have shown a significant difference between the annualised increase in the total NNSS in NPC1 participants given intrathecal HPβCD and a comparison cohort of NPC1 participants. Slowing of

disease progression was observed in NNSS ambulation, cognition, and speech subdomains. Although one might predict variable response of individual symptoms to this potential therapy and would not necessarily predict that all signs and symptoms would be amendable to HPβCD treatment, it should be noted that all major NNSS domains, excluding hearing, showed decreased progression. Future work with more patients will be required to establish what signs and symptoms are most responsive to HPβCD. Sensitivity analyses showed similar results when the analysis was restricted to participants given miglustat and were suggestive of increased efficacy with 2-week dosing. Furthermore, responder analysis showed decreased or stabilised NNSS in ten of 17 HPβCD-treated participants and disease progression in 21 of 21 comparison patients.

Some case reports have described the use of HPβCD for the treatment of NPC1. Both intravenous and intrathecal administration of HPβCD have been reported. We used lumbar intrathecal administration since HPβCD does not efficiently cross the blood–brain barrier[32] and results of preclinical studies in NPC1 cats have suggested that delivery into the CSF is three orders of magnitude more efficacious with respect to survival than peripheral dosing.[15] Intrathecal administration avoids potential pulmonary toxicity associated with high-dose systemic delivery.[15,33,34] In assessing these case reports, it should be noted that HPβCD is a complex mixture and the composition varies with the source. Thus, one cannot assume that all HPβCD formulations are equivalent with respect to either efficacy or toxicity. Matsuo and colleagues[34] reported partial and transient neurological benefit upon intravenous administration of 2–2·5 grams/kg HPβCD (Roquette Japan K.K.) in two patients with NPC1. This group attributed the absence of significant efficacy to inefficient drug delivery to the central nervous system.[35] Subsequently, they reported stabilisation of neurological disease in a single patient with NPC1 given intrathecal HPβCD up to 450 mg.[35] Garcia-Robles and colleagues[36] reported the lumbar intrathecal administration of HPβCD (175–875 mg, Trappsol) in two patients with NPC1. Drug administration was discontinued in one patient due to progression of neuropsychiatric symptoms and in the second participant after two episodes of chemical meningitis. Maarup and colleagues[37] reported improvement in VSGP and a positive 24(S)-HC response in one patient using the same HPβCD (200 mg, VTS-270) and intrathecal infusion protocol as used in this study.

This trial provides strong support for continued development of HPβCD for the treatment of NPC1 disease. In this study we document evidence for both restoration of neuronal cholesterol homoeostasis and decreased CNS pathology. The safety profile of intrathecal HPβCD is acceptable relative to the high morbidity and lethality of NPC1 disease. Most notably, by comparison with a cohort of similar age and severity, HPβCD significantly slowed neurological disease progression. Data from this trial have been accepted by the FDA to support a Breakthrough Drug designation for VTS-270, and have supported the development and implementation of a randomised, double-blind, sham-controlled, pivotal phase 2b–3 trial approved by both the FDA and EMA.

Contributors

DSO and FDP were involved in study design and implementation, data collection, data analysis, data interpretation, figure preparation and writing. EAO, MK, SAS, JCM, CHV, SUW, and CPA were involved in study design and implementation. NYF was involved in study design and implementation and data collection. KAK and CCB were involved in study design and implementation, data collection, data analysis, figure preparation, and data interpretation. XJ was involved in data collection, data analysis, and data interpretation. LW and KAW were involved in data analysis, and data interpretation. EB-K was involved in study implementation and data collection. CDD, XX, and WJP were involved in study implementation. SB, LAK, and AS were involved in data collection. RR and BNM were involved in data interpretation. RS was involved with data collection and figure preparation. AT, and BS were involved with study design and implementation, and data collection. All authors reviewed, edited, and approved the manuscript. EAO and NYF contributed equally.

Declaration of interests

DSO reports personal fees from Vtesse, outside the submitted work. DSO has a patent US Application No.: 13/786,757. Title: Methods of determining efficacy of Cyclodextrin Therapy. Inventor: Daniel S Ory and Forbes D Porter (US Patent 9,012,216) issued, and a patent US Application No.: 61/071,074. Title: Disease specific biomarkers for Niemann-Pick C Disease. Inventors: Daniel S Ory and Forbes D Porter (US Patent 8,497,122) issued. DSO and SUW are members of the Vtesse Preclinical Advisory Board. EAO reports non-financial support from Janssen Research and Development, a Johnson & Johnson company, during the conduct of the study; other from Vtesse (pre-Clinical Cooperative Research Agreement with NCATS), outside the submitted work; and is a member of the Pre-Clinical Scientific Advisory Board (PCSAB) for Vtesse as an Official Duty Activity. EB-K reports grants from Hope for Hayley Foundation, grants from Samantha's Search for the Cure Foundation, during the conduct of the study; clinical trial funding from Vtesse, a grant from Vtesse, non-financial support from Janssen R & D, outside the submitted work. EB-K is a Co-Principal Investigator on the phase 2–3 trial of intrathecal HPβCD sponsored by Vtesse. FDP reports non-financial support of this work from Vtesse, Janssen Research & Development, a Johnson and Johnson company, and Johnson & Johnson, during the conduct of the study; and has patents related to NPC biomarkers including patents 8,497,122 and 9,012,216 issued, a patent 14/776,440 pending, and a patent 61/576,062 pending. FDP is a Co-Principal Investigator on the phase 2–3 trial of intrathecal HPβCD sponsored by Vtesse. Phase 2–3 trial costs are partly offset by a Cooperative Research Agreement between Vtesse, and NICHD, NIH. FDP serves on the Vtesse Clinical NPC Advisory Committee as an Official Duty Activity. WJP has a patent 14/776,440 pending. LW reports other support from Statistics Collaborative, during the conduct of the study; other support from Statistics Collaborative, outside the submitted work. CHV reports grants and non-financial support from Janssen Pharma, grants from Ara Parseghian Medical Research Foundation, grants from Support of Accelerated Research for NPC, grants from National Niemann Pick Disease Foundation, during the conduct of the study; personal fees from Vtesse, outside the submitted work. JCM reports a patent WO 2014022841 A1 and family members licensed to Vtesse. BNM and RR are employees of Vtesse. SAS is an employee of Johnson & Johnson and MK is an employee of Janssen Research & Development, a Johnson & Johnson company. Vtesse was acquired by Sucampo in April, 2017. NYF, KAK, XJ, CDD, SB, LAK, AS, RS, KAW, XX, AT, BS, CCB and CPA declare no competing interests.

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