HHS Public Access

Author manuscript

*Lancet*. Author manuscript; available in PMC 2018 October 14.

Published in final edited form as:

*Lancet*. 2017 October 14; 390(10104): 1758–1768. doi:10.1016/S0140-6736(17)31465-4.

# Intrathecal 2-hydroxypropyl-β-cyclodextrin decreases neurological disease progression in Niemann-Pick Disease, type C1: an ad-hoc analysis of a non-randomized, open-label, phase 1/2 trial

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Contributors

DSO and FDP were involved in study design and implementation, data collection, data analysis, data interpretation, figure preparation and writing. EAO, MK, SS, JCM, CV, SUW, and CA 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. EBK was involved in study implementation and data collection. CD, XX, and WJP were involved in study implementation. SB, LK, 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.

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Ethics committee approval

Both the phase 1/2a trial of HPβCD (13-CH-0001) and the NPC1 NHx 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.

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## Abstract

**Background—**Niemann-Pick disease, type C1 (NPC1) is a lysosomal storage disorder characterized by progressive neurodegeneration. In preclinical testing 2-hydroxypropyl-β-cyclodextrins (HPβCD) significantly delayed cerebellar Purkinje cell loss, slowed progression of neurological signs, and increased lifespan in murine and feline models of NPC1.

**Methods—**Safety and clinical efficacy of intrathecal HPβCD were evaluated in an open-label, dose- escalation phase 1/2a study. Intrathecal doses ranging from 50–1200 mg were evaluated in 14 neurologically affected NPC1 participants treated monthly for 12 to 18 months. Three additional participants were treated every two weeks for 18 months. Serum and CSF 24(S)-hydroxycholesterol, which served as a biomarker of target engagement, and CSF protein biomarkers were evaluated. NPC Neurological Severity Scores (NSS) 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—**No drug-related serious adverse events were observed. Mid- to high-frequency hearing loss, an expected adverse event, was documented. When managed with hearing aids, this did not have an appreciable impact on daily communication. Biomarker studies were consistent with improved neuronal cholesterol homeostasis and decreased neuronal pathology. The NSS score for the 14 participants treated monthly increased at a rate of 122 ± 0 34 points/year compared to 2 92 ± 0 27 points/year (p=0 0002) for the comparison group. Decreased progression was observed for NSS domains of ambulation (p=0 0622), cognition (p=0 0040) and speech (p=0 0423).

**Interpretation—**This phase 1/2a study of intrathecal HPβCD for the treatment of NPC1 demonstrated an acceptable safety profile and slowing of disease progression.

## Introduction

Niemann-Pick disease, type C (NPC) is a recessive, lysosomal storage disorder characterized by endolysosomal accumulation of unesterified cholesterol.[1] NPC results from mutation of either *NPC1* or *NPC2,* with the majority of cases due to impaired NPC1 function.[2] The incidence of classical NPC disease has been estimated to be on the order of 1/100,000/.[1] The NPC1 disease phenotype is heterogeneous with respect to both age of onset and symptom complex.[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 difficulty in school. Classically, onset is in childhood, though recognition of adult cases is becoming more frequent. Cerebellar ataxia and cognitive impairment progress over years with death generally 10–15 years after onset. Other neurological symptom can include vertical supranuclear gaze palsy (VSGP), gelastic cataplexy, seizures, and high-frequency hearing loss. Although often not recognized, VSGP is typically the first neurologic symptom and along with gelastic cataplexy is indicative for NPC1 in children. Adult onset NPC1 frequently presents with psychiatric disease. NPC1 disease progression has been characterized using the NPC Neurological Severity Score (NSS). The NSS is a Likert-like scale that assesses severity of clinically relevant signs and symptoms in nine major and eight minor domains (appendix, p 10).[5-7] There are no FDA-approved therapies for NPC1 disease. Although miglustat has been approved by the EMA and other regulatory agencies based on a controlled trial and long-term extension studies,[8-10] there remains an unmet medical need for therapies that more effectively slow the neurological progression of NPC1 disease.

The potential therapeutic efficacy of 2-hydoxypropyl-β-cyclodextrins (HPβCD) was discovered serendipitously when it was used as an excipient to administer allopregnanolone in an NPC1 mouse model.[11] Subsequent studies, however, demonstrated that HPβCD, rather than the neurosteroid, was the active moiety.[12,13] Translation of this potential therapy to children with NPC1 is supported by multiple studies in both NPC1 mouse[12-14] and cat[15] models that demonstrate a marked delay in progression of neurological signs and death. Here we present the ad-hoc analysis of an 18-month non-randomized, open-label, phase 1/2a trial to determine safety and potential efficacy of escalating doses of lumbar intrathecal HPβCD in NPC1 participants.

## Methods

### Study Design, drug administration, participants, and clinical assessments

An open-label, dose-escalation study was conducted to evaluate safety, pharmacodynamics, and efficacy of monthly intrathecal doses of 50–1200 mg of a well-characterized HPβCD mixture with a specific compositional fingerprint and limits for impurities (appendix p 3, VTS-270, Vtesse Inc., Gaithersburg MD). HPβCD was formulated as a 20% solution and diluted in saline to provide an infusion volume of 10 ml, which was infused over 2–3 minutes. Details with respect to dosing are provided in the appendix (p 2 and appendix figure 2, p 11). Safety and tolerability of HPβCD was the primary objective, and 24(S)-hydroxycholesterol (24(S)-HC) response was the primary pharmacodynamic objective.

Clinical efficacy, as ascertained by the NPC Neurological Severity Scale (NSS)[6], was a secondary objective. Pharmacokinetic data will be reported separately. The study was approved by applicable Institutional Review Boards. Written informed consent was obtained.

Fourteen NPC1 disease participants with neurological manifestations between the ages of 4 2 and 23 5 years of age were enrolled at the NIH (table). The diagnosis of NPC1 disease was established by a combination of clinical, cellular and molecular criteria (appendix pp 2–3). A comparison cohort of 21 NPC1 disease participants between the ages of 4 0 and 24 0 with longitudinal evaluations was derived from the NIH Natural History (NHx) study (appendix p 2 and appendix figure 3, p 12). To explore the potential effect of every two week dosing, three additional participants were enrolled in a parallel study at Rush University Medical Center (RUMC, appendix p 2).

Severity of adverse events was graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. Audiological assessments were obtained monthly prior to each infusion. Clinical efficacy was evaluated using the NSS.[6] A detailed description of the NSS (appendix figure 1, p 5) and baseline individual NSS component scores (appendix table 1, p 11) are provided. NSS evaluations were at 18 months for participants CDA101 and CDA103–111. The 18-month evaluation for CDA112 was obtained at 19 months. NSS 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.

## Cerebral spinal fluid biomarker and pharmacodynamic assessments

Biochemical efficacy/target engagement was monitored by measurement of plasma and cerebral spinal fluid (CSF) 24(S)-HC concentrations.[16] Plasma 24(S)-HC concentrations were determined at pre-dose, 8, 24, 30, 48, and 72 hours post-dose after either saline or HPβCD infusion and the area under the curve was determined ($AUC_{8–72}$). CSF levels of fatty acid binding protein 3 (FABP3) and calbindin D were assayed by Myriad Rules Based Medicine (Austin, TX).

## Statistical Analysis

Demographic data corresponding to the HPβCD-treated cohort and the NHx cohort were compared utilizing 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 evaluate changes in 24(S)- HC, FABP3 and calbindin D levels. Spearman statistics were used to evaluate the audiological data correlations. Fisher's exact test was used for the responder analysis. Unless otherwise specified, data are expressed as mean ± SEM and a nominal p-value of 0.05 was considered significant.

No formal calculation of sample size was made for ad-hoc analysis of the NSS, and given the small sample size we are not estimating confidence intervals. A post hoc mixed model repeated measures approach was used to assess the efficacy of HPβCD in this population. The NIH NHx 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 to 24 years at the first of any two or more assessments. 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 NHx study participants), and a group by time interaction term. This approach was selected due to the limited sample size and the uneven follow up in the NIH NHx 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. The estimated average annual change or annualized slope for each group is presented as estimated from the model. The null hypothesis that the slope in the HPβCD- treated group is equal to the slope in the NHx group is assessed based on the p-value associated with the interaction term in the mixed model.

For the responder analysis, a change from baseline was used to assess the efficacy of HPβCD in individual participants. The NIH NHx population was used as the comparison group; the subject selection criteria were as described for the MMRM approach. For each domain in the NSS, the value at baseline was subtracted from the value of the same domain during the assessment at the furthest time point 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 NPCD1 NSS data and responder analysis. GraphPad Prism® was used for other statistical analysis and to generate the figures.

### Role of the funding sources

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 probono preclinical development support. Vtesse Inc. supported statistical analysis by Statistics Collaborative. FDP had full access to the data and final responsibility for the decision to submit for publication.

## Results

### Study population and HPβCD dosing

Participant demographics and clinical characteristics, participation flow, and dosing information are provided in the table, figure 1A and appendix table 1 (p 4). HPβCD was administered monthly by lumbar intrathecal infusion for the NIH participants. Dosing for CDA101–112 was initiated at 50, 200, 300, or 400 mg HPβCD in groups of 3 participants, and the dose (appendix figure 2, p 11) was advanced based on tolerance and safety data from higher dose cohorts. Mean doses at 12 and 18 months were 289 ± 68 mg and 423 ± 142 for CDA101–112, respectively. Mean dose for the initial dosing cohorts is shown in figure 1B. CDA113 and CDA114 were dosed at 900 mg for 12 months. HPβCD was administered every two weeks to the RUMC cohort and their mean dose at 18 months ranged from 297 to 481 mg (figure 1B). NIH participants were enrolled between September 2013 and January 2015. RUMC participants were enrolled between December 2013 and June 2014.

## Pharmacodynamic and Biomarker Data

In preclinical studies, treatment with HPβCD was shown to redistribute lysosomal cholesterol, resulting in modulation of a range of central nervous system (CNS) sterol homeostatic 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 homeostasis. Therefore, the drug response was monitored by measuring plasma 24(S)-HC $AUC_{8–72}$. The majority (121/155) of post-drug plasma 24(S)-HC $AUC_{8–72}$ values were greater than post-saline values; however, plasma responses were more variable and less robust compared to what was observed in preclinical testing (appendix figure 4A, pp 13–14). Despite the variability, the data suggested a trend for increased 24(S)-HC response at higher doses and significant increases in individual subject responses were observed at 900 and 1200 mg (figures 2A and2B). We also examined CSF 24(S)-HC concentrations pre- and post-HPβCD administration. The CSF 24(S)-HC concentrations in three participants treated with 600–900 mg of HPβCD were increased over two-fold (p=0 0032) 72 hours after drug administration (figure 2C). These data provide pharmacodynamic evidence of a significant response to HPβCD administration and improved neuronal cholesterol homeostasis.

Prior work demonstrated increased CSF levels 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 levels have been reported in cerebellar injury.[22] Baseline CSF FABP3 levels were significantly elevated (15 67 ± 3 38 ng/ml) over our published control levels (2 36 ± 0 72 ng/ml, p=0 0016),[18] and last treated values were significantly decreased compared to baseline (figure 2D; 8 56 ± 136 ng/ml, p=0 0109). Serial values are shown in the appendix (figure 4B, pp 13–14) and 8/14 (57%) participants demonstrated a significant negative linear regression slope, whereas no participants demonstrated a significant increase (figure 2F). Baseline CSF calbindin D levels (532 ± 69 ng/ml) were significantly increased over control values (0 76 ± 0 34 ng/ml, p=0 0001),[19] and last treated values were significantly decreased compared to baseline (figure 2E; 385 ± 56 ng/ml; p=0 0040). The majority of participants (9/14, 64%) demonstrated a significant negative linear regression slope and only one subject demonstrated a significant increase (figures 2F and appendix figure 4C, pp 13–14). These data provide evidence that treatment with HPβCD shifts, towards normal, CSF biomarkers of CNS pathology.

## Safety Assessment

No serious adverse drug reactions were observed and adverse events are tabulated in the appendix (table 3, p 6). Notable expected adverse events included participants with post lumbar puncture headache (64%, 9/14) and ototoxicity (100%, 14/14). Notable unexpected adverse events included post-administration unsteadiness and fatigue at doses above 600 mg. This was transient and typically occurred 24–72 hours after dosing. The degree of impairment was variable across participants, but classified as significant in 3/9, 6/12 and 9/9 participants at 600, 900 and 1200 mg, respectively. The unsteadiness and fatigue may variably attenuate with repetitive dosing at a given dose level. One subject presented with hepatocellular carcinoma during the trial. Hepatocellular carcinoma is a rare complication of

NPC1,[23-26] and retrospective testing revealed an increased serum level of a-fetoprotein at baseline.

Ototoxicity, likely due to outer hair cell loss,[27] following treatment with HPβCD was observed in preclinical testing.[27,28] Progressive hearing loss is observed in NPC1 disease; [29,30] however, additional hearing impairment in NPC1 participants time-locked to treatment with HPβCD was observed.

Behavioral thresholds for pure-tone stimulation could be established for 12/14 participants. Baseline and last-study audiograms are shown in figures 3A and 3B, respectively. 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 hearing aids. After HPβCD administration, all participants demonstrated additional mid- to high-frequency hearing loss, and all participants were hearing aid candidates. Change in hearing by frequency is shown in figure 3C. 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, 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 3D). These data suggest that there is greater HPβCD ototoxicity in individuals who have not yet lost hearing due to NPC1 disease itself. One subject (RUMC03) demonstrated marked sensitivity to HPβCD with CTCAE grade 3 hearing loss upon initial dosing at 400 mg; however, subsequent administration of 300 mg HPβCD every two 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 cases, but persistent in four participants.

## Clinical Efficacy Assessment

Clinical efficacy was ascertained by comparing NSS progression in the 14 NIH HPβCD-treated participants to that observed in a historical cohort of 21 participants of similar age range (table, appendix figure 3, p 12) followed in a NHx study. On average NHx patients were younger and had lower NSS at baseline, but these differences were not significant. The total NSS for the 14 participants treated monthly increased at a slower rate of 122 ± 0 34 points/year compared to 2 92 ± 0 27 points/year (p=0 0002) for the comparison cohort (figure 4A). The NSS includes components related to hearing. When the hearing related components were removed, HPβCD- treated participants showed a progression rate of 0 69 ± 0 34 versus 2 67 ± 0 27 points/year (p<0 0001) for the comparison group. These data demonstrate a significant reduction in disease progression in the HPβCD-treated cohort.

The change in the annualized slope for individual major NSS subdomains is shown in figure 4B and appendix table 4 (p 7). In comparison to the controls, the HPβCD-treated cohort demonstrated significant 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 demonstrated a notable increase (p=0 0518). Heat maps showing individual subject changes for each NSS major domain are provided for the comparison and HPβCD-treated cohorts (appendix figure 5, pp 15–16). Individual pre/post NSS for eight participants where

pretrial data were available are provided in appendix figure 6 (pp 17–18). Stabilization or slowing of NPC1 disease progression can be appreciated in six of eight participants.

Sensitivity analyses demonstrated significantly decreased progression for the total NSS (p<0 0001) as well as for ambulation (p=0 0223), cognition (p=0 0061), and speech (p=0 0218) subdomains when the analysis was restricted to participants who have been treated with miglustat (appendix table 5, p 8). When the three RUMC participants (treated every two weeks) were included in the annualized progression slope, total NSS and NSS minus hearing decreased from 1.22 to 102 and 0 69 to 0 28 points per year, respectively (appendix table 6, p 9). Significantly decreased progression was observed for ambulation (p=00117), cognition (p=0 0017) and speech (p=0 0147). In addition, a trend (p=0 0729) toward decreased progression was now observed for memory.

In a secondary responder analysis, participants in the HPβCD and NHx cohorts were classified as responders if their NSS minus hearing was stable or improved. In the NHx cohort 21/21 (100%) demonstrated disease progression (figure 4C); whereas, 7/14 (50%) of the participants in the HPβCD-treated group demonstrated disease progression (figure 4D). 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/fatigue observed in this study may be a dose-limiting side effect, especially if the dose or frequency of dosing is increased. The etiological basis of this side effect is not known. Ototoxicity was an expected adverse event based upon preclinical work.[27,28] Progressive mid- to high-frequency hearing impairment is common in NPC1 patients [29,30] and 7/17 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 impact daily communication when managed with hearing aids. Interestingly the degree of hearing loss was inversely correlated with individual participant's baseline hearing. Additional work is required to determine 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 $AUC_{8–72}$ levels increased above that observed in response to intrathecal saline administration at HPβCD doses of 900 and 1200 mg. In contrast, the increase in CSF 24(S)-HC concentration after HPβCD administration was unambiguous. These data provide pharmacodynamic support for mobilization of stored cholesterol in CNS neurons in response to treatment with HPβCD. We also observed that CSF calbindin D and FABP3 levels, biomarkers of neuronal damage, decreased significantly in the majority of HPβCD-treated participants. Neither calbindin D nor FABP3 have been established as clinical surrogates, but our observation that CSF levels decrease in temporal relationship with HPβCD therapy is

consistent with the conclusion that intrathecal HPβCD decreases neuronal damage in NPC1 participants.

In this study we explored monthly intrathecal doses between 50 and 1200 mg. Scaling based on brain size from the cat model to humans would suggest increased efficacy with higher and more frequent (every two week) doses.[15] The limited data available from the RUMC participants suggests that every two week dosing may be more effective than monthly dosing. Although higher and more frequent dosing may prove to be more efficacious, ultimately this will be a balance between efficacy and tolerability of the side effects. Because patient numbers are limited in this rare disease, we elected to explore higher and more frequent dosing in the context of a placebo-controlled phase 2b/3 trial.

This study has several limitations. First, it relies on a historical comparison group, and is not a randomized, placebo-controlled trial. Second, the clinical efficacy data is based upon an ad-hoc analysis. Third, the dose escalation design focused on determining safety and tolerability limits our ability to establish dose-response correlations with biomarker and clinical data. Nonetheless, the results presented in this report provide compelling evidence that intrathecal HPβCD therapy significantly decreases neurological disease progression in NPC1 patients. Specifically, we have shown that there is a significant difference between the annualized increase in the total NSS in NPC1 participants treated with intrathecal HPβCD and a comparison cohort of NPC1 participants. Slowing of disease progression was observed in NSS 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/symptoms would be amendable to HPβCD treatment, it should be noted that all major NSS domains, excluding hearing, showed decreased progression. Future work with increased numbers of patients will be required to determine what signs/symptoms are most responsive to HPβCD. Sensitivity analyses showed similar results when the analysis was restricted to participants treated with miglustat and were suggestive of increased efficacy with every two week dosing. Furthermore, a responder analysis showed decreased or stabilized NSS in 10/17 HPβCD-treated participants while 21/21 comparison subjects demonstrated disease progression.

A number of case reports have described the use of HPβCD for the treatment of NPC1. Both intravenous and intrathecal administration of HPβCD have been reported. We elected to use lumbar intrathecal administration since HPβCD does not efficiently cross the blood-brain-barrier[31] and preclinical studies in the NPC1 cat model have demonstrated that delivery into the CSF is three orders of magnitude more effective with respect to survival than peripheral dosing.[15] In addition, intrathecal administration avoids potential pulmonary toxicity associated with high-dose systemic delivery.[15,32,33] In evaluating 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 et al[33] reported partial and transient neurological benefit upon intravenous administration of 2–2.5 grams/kg HPβCD (Roquette Japan K.K.) in two NPC1 patients. This group interpreted the lack of significant efficacy to inefficient drug delivery to the central nervous system.[34] Subsequently, they reported stabilization of neurological disease in a single NPC1 patient treated by intrathecal administration of up to

450 mg HPβCD.[34] Garcia-Robles et al reported the lumbar intrathecal administration of HPβCD (175–875 mg, Trappsol®) in two NPC1 subjects.[35] Drug administration was discontinued in one subject due to progression of neuropsychiatric symptoms and in the second subject after two episodes of chemical meningitis. Maarup et al reported improvement in VSGP and a positive 24(S)-HC response in one patient utilizing the same HPβCD (200 mg, VTS-270) and intrathecal infusion protocol as used in this study.[36]

This phase 1/2a trial of intrathecal HPβCD 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 homeostasis and decreased CNS pathology. The safety profile of intrathecal HPβCD is acceptable relative to the high morbidity and lethality of NPC1 disease. Most notably, in comparison to a comparison cohort of similar age and severity, HPβCD significantly slows 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 randomized, sham-controlled, pivotal phase 2b/3 trial approved by both the FDA and EMA.

## 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 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 NiemannPick disease, type C1 (NPC1) by the EMA and other regulatory agencies but not the FDA. 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 evaluate the safety and efficacy of intrathecal 2-hydroxypropyl-P-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 NiemannPick disease, type C1 is a critical unmet medical need. In this study we provide an ad-hoc 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

ad-hoc analysis indicates a decreased rate of neurological disease progression in the treated cohort. Evaluation of biomarkers provided additional support for improved neuronal cholesterol homeostasis 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 homeostasis, biomarker data suggestive of decreased neuronal damage, and decreased neurological progression in treated participants. This study provides the rationale to proceed to a phase 2b/3 study. Data from a multicenter, international, randomized, sham-controlled phase 2b/3 study will be needed to confirm the results of this study and obtain FDA and EMA approval.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgements

The authors express their appreciation to the caregivers and patients who participated in this study, to all the members of the NPC1 community who contributed to this effort, and to the family organizations that provided support: Ara Parseghian Medical Research Foundation, Dana's Angels Research Trust, Hadley Hope Fund, Hope for Hayley, Hide & Seek Foundation, International Niemann-Pick Disease Alliance, National Niemann-Pick Disease Foundation, Samantha's Search for the Cure, Support Of Accelerated Research for NPC Disease, and The Addi & Cassi Fund. This work was supported by funding from the Intramural Research Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (FDP), the National Institute on Deafness and Other Communication Disorders (CCB), and the National Center for Advancing Translational Science (EAO, CPA, XX and JM), NIH, DHHS, and by NIH Grants R01 NS081985 (DSO) and R01 NS073661 (CHV) and by contract HHSN261200800001E from NCATS/NCI (DSO). Support was provided by grants from the Dana's Angels Research Trust (DSO and FDP), Ara Parseghian Medical Research Foundation (FDP, CHV), Hope for Hayley and Samantha's Search for the Cure Foundations (EBK), National Niemann-Pick Disease Foundation (CHV) and Support Of Accelerated Research for NPC Disease (DSO, SUW, CDD and CHV). Data management was supported by the NICHD Clinical Trials Database Team. The authors are deeply appreciative for the assistance provided by numerous individuals who contributed to the successful completion of this study. These include Marcus Brewster, Karim Calis, Jamie Chin, Stephanie Cologna, James Cradock, Nuria Carrillo-Carrasco, Cristina Csimma, Hope Decederfelt, Marc DeMeulder, Cristan Farmer, George Grimes, Alan Hubbs, Marjo Janssen, Roopa Kanakatti-Shankar, Kristen Lewis, Aiyi Liu, Leonza Machielse, Juan Marugan, Lili Portilla, Ilona Scott, Judith Starling, Sury Vepa, Chris Zalewski, and Wei Zheng. HPβCD was provided by Janssen Research & Development, a Johnson & Johnson company. The authors and the NPC community are indebted to Johnson & Johnson for their support in helping to move the initial development of this drug forward. To Dillon, a kid who showed us how to live life in spite of a devastating disease.

Funding

National Institutes of Health, Dana's Angels Research Trust, Ara Parseghian Medical Research Foundation, Hope for Haley, Samantha's Search for the Cure Foundation, National NiemannPick Disease Foundation, Support of Accelerated Research for NPC Disease, Vtesse, Inc., Janssen Research and Development, a Johnson & Johnson company, and Johnson & Johnson.

## Declaration of interests

Dr. Ory reports personal fees from Vtesse Therapeutics, outside the submitted work. In addition, Dr. Ory has a patent U.S. 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 U.S. 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. Drs. Ory and Walkley are members of the Vtesse Preclinical Advisory Board. Dr. Ottinger reports non-financial support from Janssen Research and Development, a Johnson & Johnson company, during the conduct of the study; other from Vtesse, Inc. (pre-Clinical Cooperative Research Agreement with NCATS), outside the submitted work; and Elizabeth Ottinger is a member of the Pre-Clinical Scientific Advisory Board (PCSAB) for Vtesse, Inc. as an Official Duty Activity. Dr. Berry-Kravis 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 Inc., a grant from Vtesse Inc., non-financial support from Janssen R & D, outside the submitted work. Dr. Berry-Kravis is a Co-Principal Investigator on the phase 2/3 trial of intrathecal HPβCD sponsored by Vtesse. Dr. Porter reports non-financial support of this work from Vtesse, Inc, Janssen Research & Development, a Johnson and Johnson company, and Johnson & Johnson, during the conduct of the study; In addition, Dr. Porter 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. He is a Co-Principal Investigator on the phase 2/3 trial of intrathecal HPβCD sponsored by Vtesse. Phase 2/3 trial costs are partially offset by a Cooperative Research Agreement between Vtesse, Inc. and NICHD, NIH. Dr. Porter serves on the Vtesse Clinical NPC Advisory Committee as an Official Duty Activity. Dr. Pavan has a patent 14/776,440 pending. Dr. Weissfeld reports other support from Statistics Collaborative, during the conduct of the study; other support from Statistics Collaborative, outside the submitted work. Dr. Vite 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. Dr. McKew reports a patent WO 2014022841 A1 and family members licensed to Vtesse. Drs. Machielse and Rao are employees of Vtesse. Dr. Steven Silber is an employee of Johnson & Johnson and Dr. Mark Kao is an employee of Janssen Research & Development, a Johnson & Johnson company. Other authors declare no competing interests.

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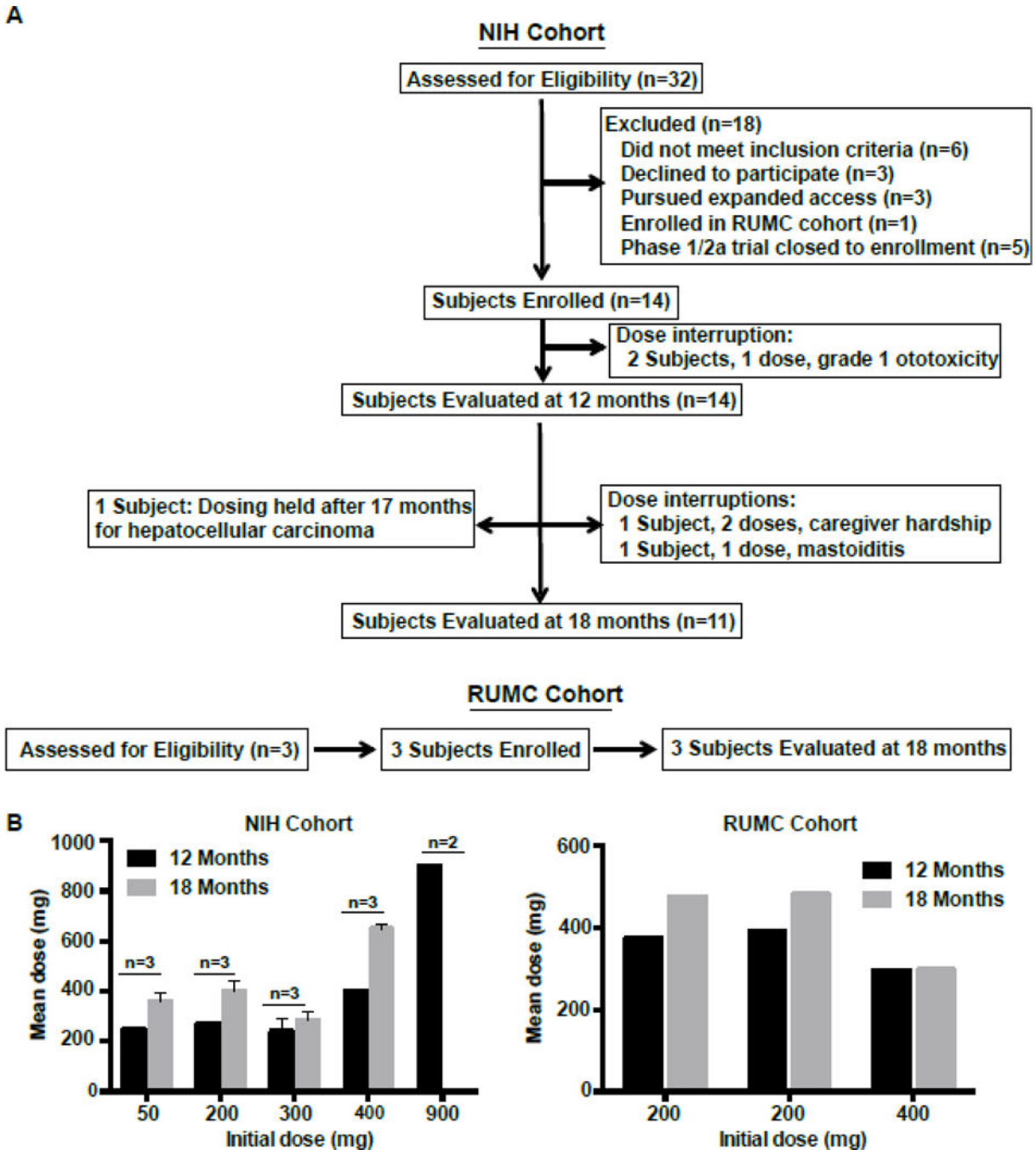


**Figure 1. Study participants and HPβCD dosing**

(A) Enrollment of participants at the NIH Clinical Center (n=14) between September 2013 and January 2015 and participants at RUMC (n=3) between December 2013 and June 2014. Intrathecal HPβCD was administered monthly in the NIH cohort and every two weeks in the RUMC cohort. (B) Mean HPβCD dose for the NIH cohorts and RUMC participants at 12 (black bars) and 18 (gray bars) months. NIH participants were enrolled in 5 cohorts with escalating initial doses.

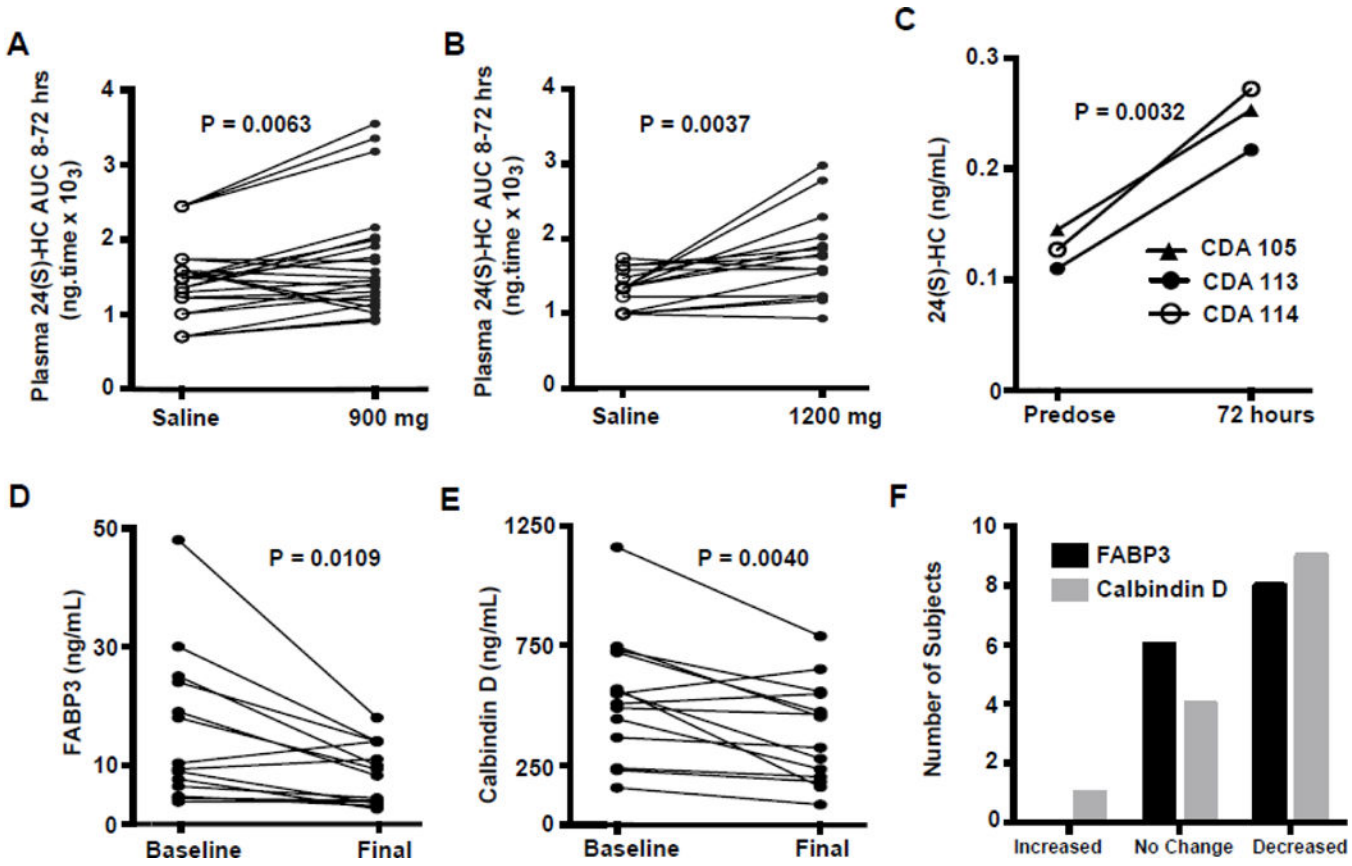


**Figure 2. 24(S)-hydroxycholesterol and cerebrospinal fluid biomarker responses**

Plasma 24(S)-HC $AUC_{8–72\ hrs}$ values increased after intrathecal doses of 900 mg (A) or 1200 mg (B) of HPβCD relative to the values observed after intrathecal infusion of saline. Each paired set of pre/post values represents an individual dose: for 900 mg, n=18 doses among 8 subjects; for 1200 mg, n=13 doses among 7 subjects. (C) CSF 24(S)-HC concentration measured prior to and 72 hours after drug administration in three participants. A significant increase in CSF 24(S)-HC levels was observed. Significant decreases were observed when comparing baseline and final CSF FABP3 (D) and calbindin D (E) levels. (F) Histogram plot of the distribution of individual subject CSF FABP3 and calbindin D responses to monthly administration of HPβCD.

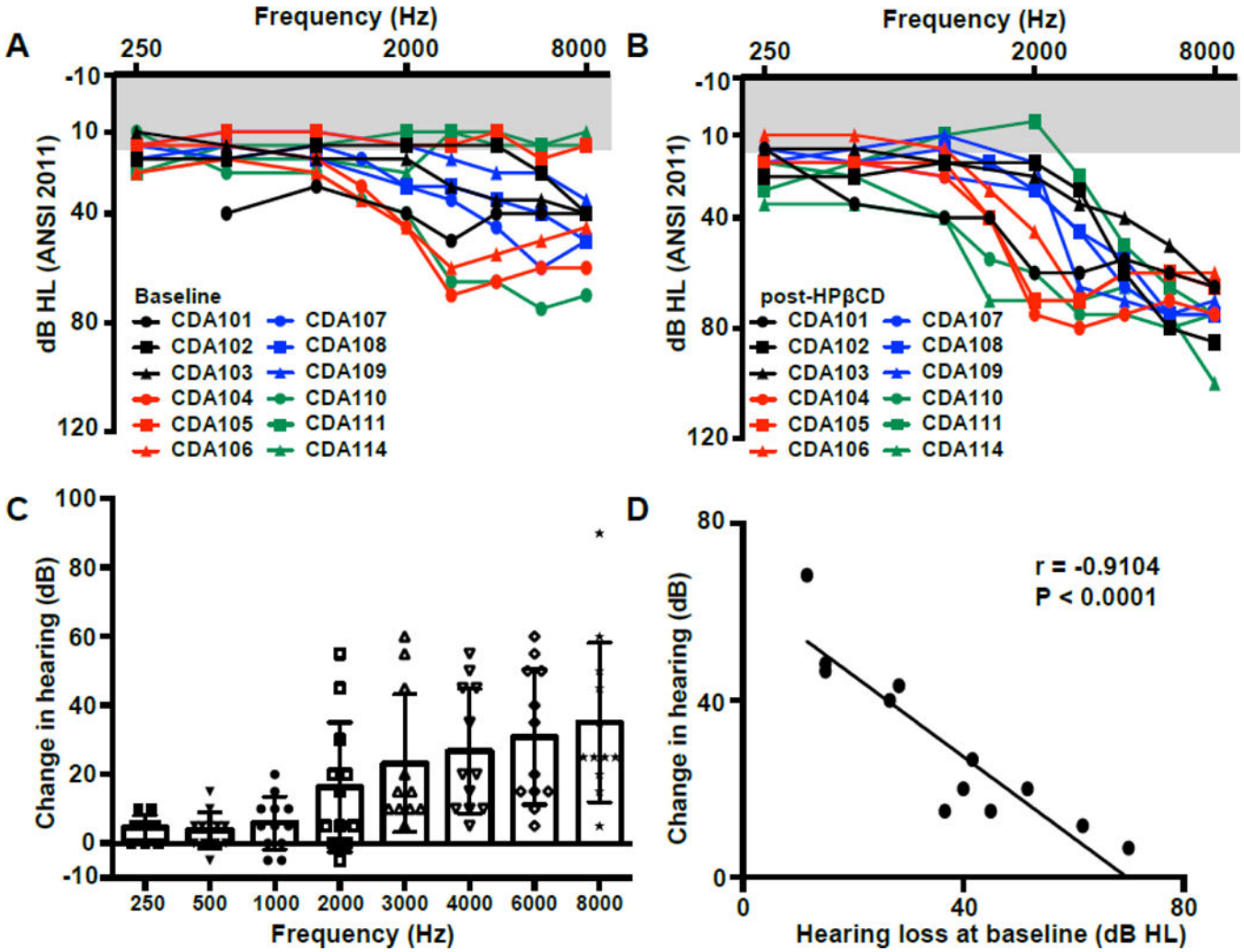


**Figure 3. Characterization of audiological effects of intrathecal HPβCD**

Pre-study (A) and last-study (B) behavioral audiograms are shown for individual participants. Behavioral audiograms could not be obtained on participants CDA112 and CDA113 due to inability of these participants to perform this testing. Data shown are from the most affected ear. The shaded gray region denotes the range of normal hearing sensitivity.[37] (C) Change in hearing from pre-study to last-study evaluation plotted by frequency. (D) Pre- to last-study hearing change correlated with the level of preexisting hearing loss at baseline for 4/6/8 kHz pure-tone average.

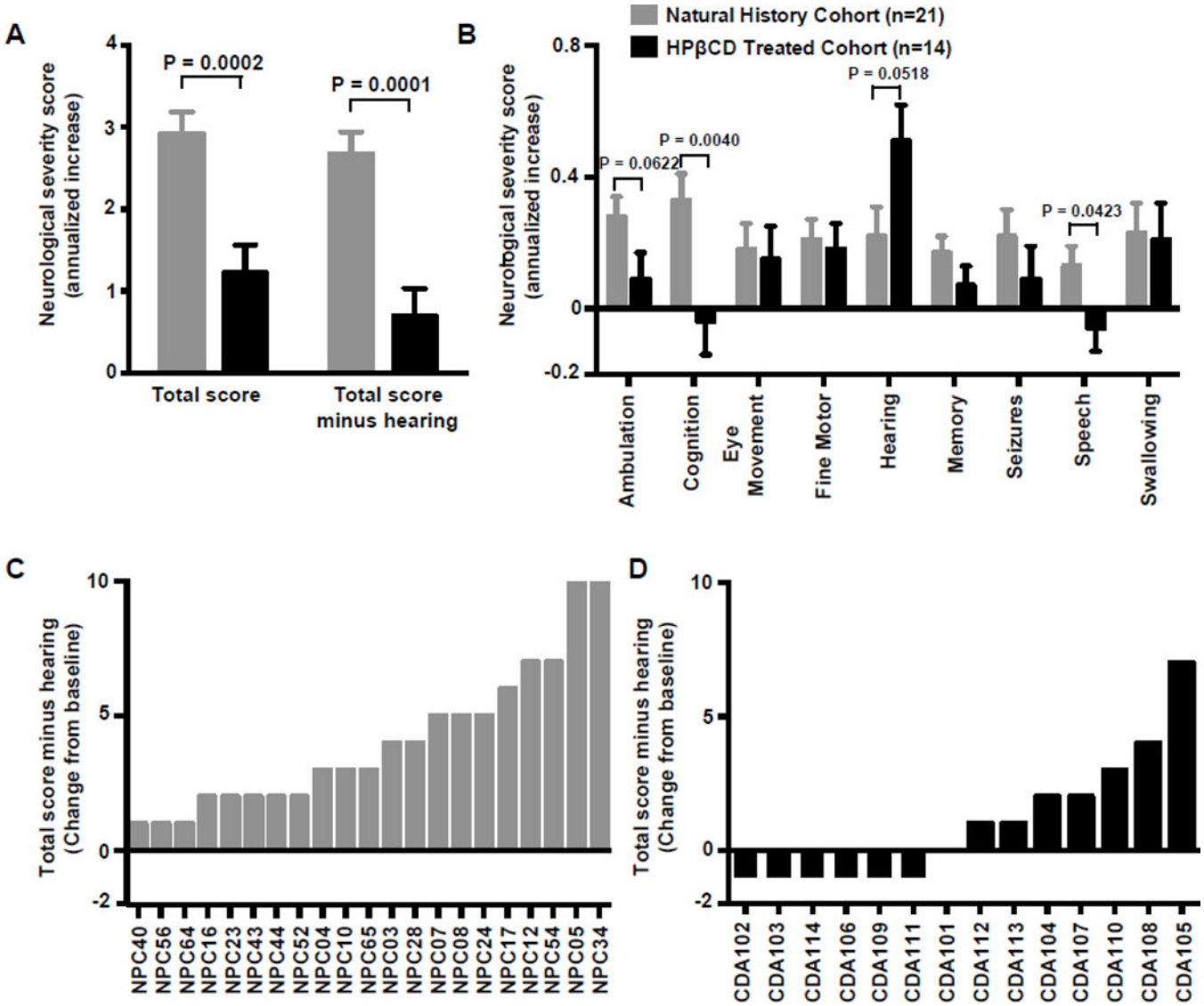


**Figure 4. Clinical efficacy of intrathecal HPβCD**

NPC Neurological Severity Scores (NSS) were used to characterize NPC1 disease progression in 21 NHx patients (gray bars) and 14 HPβCD-treated participants (black bars). (A) Significant decreased annualized rate of disease progression, as ascertained by the Total NSS and Total NSS minus hearing components, in HPβCD-treated participants compared to the comparison NHx patients. Data are from the 12- month evaluation for CDA102, CDA113 and CDA114, and from the 18-month evaluation for CDA101 and CDA 103–112. Evaluation of the individual major components of the NSS (B). Annualized rate of disease progression is decreased for ambulation, cognition, and speech in the intrathecal HPβCD-treated participants in comparison to the NHx group. Only the hearing subdomain demonstrated a notable annualized increase in progression in the HPβCD-treated group. This is consistent with the known ototoxicity of HPβCD. A responder analysis was performed based on the change from baseline in the NSS in the NHx patients (C) and the HPβCD-treated (D) participants. Individuals with a decreased or stable NSS minus hearing

were considered to be responders. Progression was observed in 21/21 NHx patients; whereas, only 7/14 HPβCD-treated participants demonstrated disease progression (p=0 0005).

Participant Demographics and Clinical Characteristics

| Characteristic | Natural History Cohort (n=21) | NIH HPβCD Treated Cohort (n=14) | p-value |
|---|---|---|---|
| Age at baseline - years | | | |
| Mean* | 10.7 ± 60 | 1.51 ± 5.5 | 0.61 |
| Median (range) | 10.0 (4.0–21.09) | 14 6 (4–2-23–5) | |
| Sex number (%) | | | |
| Male | 9(43) | 7(50) | 0.73 |
| Female | 12(57) | 7(50) | |
| Total NSS at baseline - points | | | |
| Mean | 14.5 ± 9.7 | 19.3 ± 7.5 | 0.72 |
| Median (range) | 14 (1–35) | 19(5–32) | |
| Total NSS-hearing at baseline - points | | | |
| Mean | 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 | 2.3 ± 3.7 | 3.5 ± 43 | 0.83 |
| Median (range) | 0.6 (0.0–13.0) | 1.0 (0.0–12.0) | |
| Age of first neurological symptom – years | | | |
| Mean | 5.4 ± 4.2 | 5.9 ± 3.5 | 0.93 |
| Median (range) | 3.5 (1.2–15.0) | 6.0 (1.0–1.2) | |
| Age of diagnosis – years | | | |
| Mean | 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 - number (%) | | | |
| Yes | 16 (76) | 12 (86) | 0.68 |
| No | 5 (24) | 2 (14) | |

* ± SEM