Supplementary appendix

Ory et al. Intrathecal 2-hydroxypropyl-β-cyclodextrin decreases neurological disease progression in Niemann-Pick Disease, type C1

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METHODS

Study design, dosing and implementation

NIH Participants

Fourteen participants were enrolled at the NIH Clinical Center between September 2013 and January 2015. Cohort size was three participants for initial intrathecal (IT) doses of 50 mg (CDA101-103), 200 mg (CDA104-106), 300 mg (CDA107-109) and 400 mg (CDA110-112). Individual dosing and individual mean dose information is provided in supplemental figure XX. Three participants (CDA101-103) were initially dosed with 50 mg via an Ommaya reservoir approximately 6 months prior to initiation of the intrathecal trial. Use of the Ommaya reservoirs was discontinued due to *P. acnes* infection/colonization in two subjects. Two participants (CDA113-114) were initially dosed at 900 mg and purposely maintained at a dose of 900 mg for 12 months to obtain long-term information about this dose. After initial dosing at the specified cohort dose, participants were dose-escalated as tolerated. Siblings (CDA107 and CDA108) experienced grade 1 ototoxicity with administration of the first dose of 300 mg. Dose escalation was slower in these two participants with a maximal dose of 400 mg. CDA109, who was in the same dosing cohort, was not escalated above 400 mg due to parental concern about ototoxicity. For these reasons the mean dose in the 300 mg cohort at 18 months is low (Figure 1B). For other subjects, subsequent dose-escalations included IT doses of 600 and 1200 mg HPβCD. By 18 months three subjects (CDA102, CDA104, CDA105) had received at least one dose of 600 mg; three subjects (CDA101, CDA103, CDA106) were dose escalated to 900 mg, and three subjects (CDA110, CDA111, CDA112) were receiving 1200 mg. This study was approved by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Institutional Review Board. Written informed guardian permission or subject consent was obtained. Assent was obtained when possible. This study was registered on ClinicalTrials.gov (NCT01747135) prior to participant enrollment. Study monitoring was provided by a study safety committee and an independent Data Safety Monitoring Board. Independent auditing was provided by Amarex Clinical Research (Gaithersburg, MD). An investigator IND supported the study (IND 113273). This IND was subsequently transferred to Vtesse, Inc. (Gaithersburg, MD) to support further drug development. Vtesse supported statistical analysis of the study data.

The Natural History cohort was evaluated at the NIH Clinical Center. This study (NCT00344331) was approved by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Institutional Review Board. Written informed guardian permission or subject consent was obtained. Assent was obtained when possible.

RUMC participants

Three participants were enrolled at Rush University Medical Center (RUMC) between December 2013 and June 2014 under an expanded access IND. The study protocol was approved by the RUMC Institutional Review Board. Written informed consent was obtained. Demographics and clinical characteristics for these participants are provided in Supplemental Table 5. Dosing was initiated at 200 mg for the first two participants and then 400 mg for the third. HPβCD administration was every two weeks. Safety and efficacy assessments were similar to those obtained at the NIH. Adverse events were also scored by CTCAE criteria and audiological assessments were obtained every 2 weeks for (RUMC-01 and RUMC-02) and the first 15 months

(RUMC-03) of treatment. Of the 120 scheduled doses, one dose (IT3 for RUMC-03) was held due to hearing loss.

Diagnostic Criteria

Diagnosis of NPC1 was established based upon one of the following:

a. Two NPC1 mutations;
b. Positive filipin staining and at least one NPC1 mutation;
c. Vertical supranuclear gaze palsy (VSNGP) in combination with either:
    i. One NPC1 mutation, or
    ii. Positive filipin staining and no NPC2 mutations.

VTS-270 specifications and drug administration

HPβCD is a cyclic oligosaccharide with a distinctive truncated cone configuration containing 7-cyclo-α-(1,4)-anhydroglucose units with hydroxypropyl groups randomly substituted onto the C-2, C-3, and C-6 positions of the molecule. VTS-270 is a specific and well-characterized mixture of HPβCD. The level of hydroxypropylation is strictly controlled during manufacturing, resulting in a drug with a tightly controlled molar substitution specification (of 0.58-0.68) and a defined fingerprint of the different species present in the mixture. Critical unique specifications, tighter than the USP/EP for HPβCD have been established. The USP/EP specifications were developed for use as a drug excipient. The specifications include levels of impurities such as endotoxin, propylene glycol and unsubstituted cyclodextrin.

For NIH participants the IT injection was typically performed monthly (± 1 week) in the L4/L5 interspace after removal of 10 ml of cerebral spinal fluid (CSF). For RUMC participants intrathecal infusions were typically performed in the L4/L5 or L5/S1 interspace after removal of 10 ml of CSF and participants were placed in Trendelenburg position for 60 minutes after administration.

Appendix Table 1. Baseline Neurological Severity Scores

	AGE (years)	EYE MOVEMENT	AMBULATION	SPEECH	SWALLOW	FINE MOTOR	COGNITION	HEARING	MEMORY	SEIZURES	CATAPLEXY	NARCOLEPSY	BEHAV	PSYCH	HYPERREFLEXIA	INCONTINENCE	RESPIRATORY
2-hydroxypropyl-beta-cyclodextrin treated group																	
CDA101	13.6	2	1	1	2	1	3	2	1	0	0	0	0	0	2	0	0
CDA102	11.1	2	2	2	1	4	3	2	3	0	2	0	0	0	2	0	0
CDA103	21.5	3	2	1	2	2	3	2	1	0	0	0	0	0	2	0	0
CDA104	14.6	2	2	2	5	2	3	3	1	3	1	0	0	0	2	0	0
CDA105	23.5	3	4	2	4	4	4	2	2	0	2	0	0	1	2	0	0
CDA106	14.5	2	1	2	1	1	3	3	1	5	0	0	0	0	1	0	0
CDA107	18.0	2	2	1	2	2	3	3	1	0	0	0	0	0	2	0	0
CDA108	13.9	2	1	1	0	1	3	1	1	3	0	0	0	0	1	0	0
CDA109	22.6	2	1	1	2	1	3	1	1	0	0	0	1	1	1	0	0
CDA110	16.5	2	2	1	0	2	3	3	1	0	0	0	0	0	2	0	0
CDA111	8.0	1	1	0	1	1	3	1	0	0	0	0	0	0	0	0	0
CDA112	10.7	2	2	2	1	1	4	0	2	3	0	0	1	0	2	1	0
CDA113	18.4	2	4	3	5	5	3	0	3	3	2	0	0	0	0	2	0
CDA114	4.2	3	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0
NIH natural history study control group																	
NPC03	13.1	5	5	3	4	4	3	0	3	3	1	0	0	0	0	1	0
NPC04	5.0	3	0	1	0	0	1	1	3	0	0	0	0	0	0	1	0
NPC05	10.0	3	1	1	0	2	1	1	1	0	1	0	1	0	0	1	0
NPC07	11.8	5	2	1	2	2	3	1	1	0	2	0	0	0	1	1	1
NPC08	4.0	3	2	3	0	4	5	1	3	0	1	0	0	0	1	2	0
NPC10	11.9	2	1	1	1	1	3	2	2	0	2	0	0	0	0	0	2
NPC12	4.7	2	2	2	0	2	1	1	1	0	0	0	0	0	0	0	0
NPC16	4.7	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0
NPC17	6.2	2	1	1	0	1	1	0	1	0	0	0	0	0	0	0	0
NPC23	7.7	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
NPC28	4.8	2	1	1	0	0	0	1	1	0	0	0	0	0	0	0	0
NPC34	4.4	3	2	2	0	4	3	1	0	3	2	0	0	0	1	0	0
NPC40	4.7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
NPC43	8.2	2	1	1	0	1	1	0	0	0	0	0	0	0	1	0	1
NPC44	20.4	3	1	1	1	0	3	0	1	0	2	0	1	0	0	0	0
NPC52	15.6	2	1	1	0	2	3	1	0	0	0	0	0	0	1	1	0
NPC54	17.2	2	1	1	2	1	3	2	2	0	0	0	1	2	0	0	1
NPC64	12.5	2	1	0	0	2	4	1	3	5	0	0	1	0	1	0	0
NPC65	13.7	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
NPC24	21.5	3	5	3	5	5	5	1	3	0	0	0	0	1	1	2	0
NPC56	21.9	2	1	1	2	1	4	0	2	0	0	0	1	1	2	1	0

Appendix Table 2. RUMC Participant Demographics and Clinical Characteristics

	RUMC-01	RUMC-02	RUMC-03
Age at baseline (years)	14	15	17
Sex	Female	Male	Female
Total NSS at baseline (points)	31	2	11
Total NSS minus hearing at baseline (points)	31	2	10
Age of first NP-C symptom (years)	6	13	10
Age of first neurological symptom (years)	6	13	10
Age of diagnosis (years)	12	13	16
Miglustat use	Yes	Yes	Yes

Appendix Table 3. Selected Adverse Events

Event	NIH Subjects (N=14)	RUMC Subjects (N=3)
Ear and labyrinth events – no. (%)		
Sensorineural hearing loss	14 (100)	2 (67)
Tinnitus	6 (43)	1 (33)
Post-procedure complications – no. (%)		
Headache	9 (64)	1 (33)
Fatigue	8 (57)	2 (67)
Vomiting	7 (50)	1 (33)
Increased clumsiness, ataxia	5 (36)	1 (33)
Lower back pain	4 (29)	-
Local discomfort at LP site	3 (21)	-
Neurological events – no. (%)		
Seizure	5 (36)	-
Paresthesia	2 (14)	-
Cough or dysphagia	2 (14)	-
Gastrointestinal/genitourinary events – no. (%)		
Transient elevation of liver enzymes	5 (36)	-
Bowel incontinence	4 (29)	-
Diarrhea	3 (21)	1 (33)
Transient proteinuria	2 (14)	-
Transient urobilinogen	2 (14)	-
Nocturia	2 (14)	-
Inflammatory/Infectious events – no. (%)		
Fever	4 (29)	1 (33)
Otitis media/externa	3 (21)	-
Sinusitis/Upper respiratory infection	2 (14)	3 (100)
Infectious enterocolitis	1 (7)	1 (33)
Respiratory events – no. (%)		
Aspiration or aspiration pneumonia	2 (14)	-
Laryngospasm during anesthesia	1 (7)	-
Trauma events – no. (%)		
Fracture	2 (14)	-
Laceration	-	1 (33)

Appendix Table 4. Annualized Progression Slope for the 14 HPβCD Treated Participants Compared to 21 Natural History Patients

	Natural history annualized slope (SE) N =21	HPβCD treated annualized slope (SE) N = 14	F-test p value for equal slopes N = 35
NPC-CSS Ambulation	0.28 (0.06)	0.09 (0.08)	0.0622
NPC-CSS Fine motor	0.21 (0.06)	0.18 (0.08)	0.81
NPC-CSS Cognition	0.33 (0.08)	-0.04 (0.10)	0.0040
NPC-CSS Swallowing	0.23 (0.09)	0.21 (0.11)	0.88
NPC-CSS Memory	0.17 (0.05)	0.07 (0.06)	0.24
NPC-CSS Eye movement	0.18 (0.08)	0.15 (0.10)	0.82
NPC-CSS Speech	0.13 (0.06)	-0.06 (0.07)	0.0423
NPC-CSS Hearing	0.22 (0.09)	0.51 (0.11)	0.0518
NPC-CSS Seizures	0.22 (0.08)	0.09 (0.10)	0.28
NPC-CSS Total	2.92 (0.27)	1.22 (0.34)	<0.0002
NPC-CSS Total minus hearing/ABR	2.67 (0.27)	0.69 (0.34)	<0.0001

Appendix Table 5. Annualized Progression Slope for Participants Treated with Miglustat

	Miglustat treated Natural History patients annualized slope (SE) N = 16	HPβCD and miglustat treated participants annualized slope (SE) N = 12	F-test p-value for equal slopes N = 28
NPC-CSS Ambulation	0.27 (0.06)	0.05 (0.07)	0.0223
NPC-CSS Fine motor	0.14 (0.07)	0.15 (0.08)	0.97
NPC-CSS Cognition	0.36 (0.09)	-0.04 (0.11)	0.0061
NPC-CSS Swallowing	0.27 (0.10)	0.18 (0.12)	0.54
NPC-CSS Memory	0.20 (0.06)	0.08 (0.07)	0.20
NPC-CSS Eye movement	0.18 (0.06)	0.01 (0.08)	0.0922
NPC-CSS Speech	0.16 (0.06)	-0.08 (0.08)	0.0218
NPC-CSS Hearing	0.26 (0.10)	0.53 (0.13)	0.11
NPC-CSS Seizures	0.26 (0.09)	0.10 (0.11)	0.25
NPC-CSS Total	3.10 (0.27)	0.87 (0.33)	<0.0001
NPC-CSS Total minus hearing/ABR	2.80 (0.27)	0.31 (0.33)	<0.0001

Appendix Table 6. Annualized Progression Slope Including both NIH and RUMC Participants

	Natural history annualized slope (SE) N = 21	HPβCD treated annualized slope (SE) N = 17	F-test p-value for equal slopes N = 38
NPC-CSS Ambulation	0.28 (0.06)	0.00 (0.08)	0.0117
NPC-CSS Fine motor	0.21 (0.06)	0.13 (0.07)	0.43
NPC-CSS Cognition	0.33 (0.08)	-0.03 (0.09)	0.0017
NPC-CSS Swallowing	0.23 (0.09)	0.07 (0.12)	0.30
NPC-CSS Memory	0.17 (0.05)	0.02 (0.06)	0.0729
NPC-CSS Eye movement	0.18 (0.08)	0.13 (0.09)	0.67
NPC-CSS Speech	0.13 (0.06)	-0.09 (0.07)	0.0147
NPC-CSS Hearing	0.22 (0.09)	0.63 (0.11)	0.0066
NPC-CSS Seizures	0.22 (0.08)	0.07 (0.08)	0.19
NPC-CSS Total	2.92 (0.27)	1.02 (0.33)	<0.0001
NPC-CSS Total minus hearing/ABR	2.67 (0.27)	0.28 (0.35)	<0.0001

Appendix Figure 1. NPC Neurological Severity Score Case Report Form.

NPC Severity Scale

Study of IT HPβCD for NPC1 | Protocol No: 13-CH-0001 | Visit _____
Subject ID: _____ | Date _____(mm/dd/yy) | Scored by_____

Eye Movement	Score
Normal eye movement	0
Mild vertical supranuclear gaze palsy (VSGP), detected by physician only	1
Functional VSGP, noted by family or pt compensates with head movements	2
Total VSGP, some abnormal horizontal saccades may be present	3
Total ophthalmoplegia (vertical and horizontal saccades absent)	5

Speech	Score
Normal speech	0
Mild dysarthria (understood by others)	1
Severe dysarthria (understood by family only)	2
Non-verbal/functional communication skills for needs	3
Absence of communication	5

Fine Motor Skills	Score
Normal	0
Slight dysmetria/dystonia (independent manipulation)	1
Mild dysmetria/Dystonia (requires little to no assistance, able to feed self without difficulty)	2
Moderate dysmetria/dystonia (limited fine motor skills, difficulty feeding self)	4
Severe dysmetria/Dystonia (gross motor limitation, requires assistance for all activities)	5

Hearing	Score
Normal hearing (all tones ≤ 15 dB HL)	0
High frequency sensineural hearing loss (PTA** ≤ 15 dB HL, > 15 dB HL in high frequencies)	1
Slight-mild sensineural hearing loss (PTA 16-44 dB HL)	2
Moderate sensineural hearing loss (PTA 45-70 dB HL)	3
Severe hearing loss (PTA 71-90 dB HL)	4
Profound hearing loss (PTA > 90 dB HL)	5

Seizures	Score
No history of seizures	0
Single seizure	1
Rare seizures	2
Seizures, well controlled with meds	3
Seizures, difficult to control with meds	5

Modifiers	Score
Gelastic Cataplexy	
No history	0
Definitive history	+1
Frequent (every month)	+2
Narcolepsy	
No history	0
Definitive history	+1
Frequent (every month)	+2
Behavior	
No problems	0
Hx ADHD, aggressive	+1
Harmful to self/others	+2

Ambulation	Score
Normal	0
Clumsy	1
Ataxic unassisted gait or not walking by 18mos	2
Assisted ambulation or not walking by 24 months	4
Wheelchair dependent	5

Swallow		Score
Normal, no dysphagia		0
Cough while eating		1
Intermittent dysphagia*	w/Liquids	+1
	w/Solids	+1
Dysphagia*	w/Liquids	+2
	w/Solids	+2
Nasogastric tube or gastric tube for supplemental feeding		4
Nasogastric tube or gastric tube feeding only		5

Cognition	Score
Normal	0
Mild learning delay, grade appropriate for age	1
Moderate learning delay, individualized curriculum **or** modified work setting	3
Severe delay/plateau, some loss of cognitive function, no longer in school **or** no longer able to work	4
Minimal cognitive function	5

Memory	Score
Normal	0
Mild short-term **or** long-term memory loss (forgetful)	1
Moderate short-term **or** long-term memory loss (gets lost)	2
Difficulty following commands	3
Unable to follow commands **or** short- **and** long-term memory loss	4
No memory	5

Modifiers	Score
Psychiatric	
No problems	0
Hx of mild depression	+1
Hx of major depression, Hallucinations, psychotic episodes	+2
Hyperreflexia	
None	0
Mild	+1
Severe (+ clonus)	+2
Incontinence	
No problems	0
Occasional	+1
Frequent	+2
Auditory Brainstem Response (ABR)	
Normal	0
Abnormal	+1
Absent	+2
Respiratory	
No problems	0
Hx pneumonia	+1
Pneumonia ≥ 2x/year or active therapeutic intervention	+2

* Score is additive within these two subsections
** PTA = pure-tone average – this is reported on the audiogram

TOTAL SCORE _____

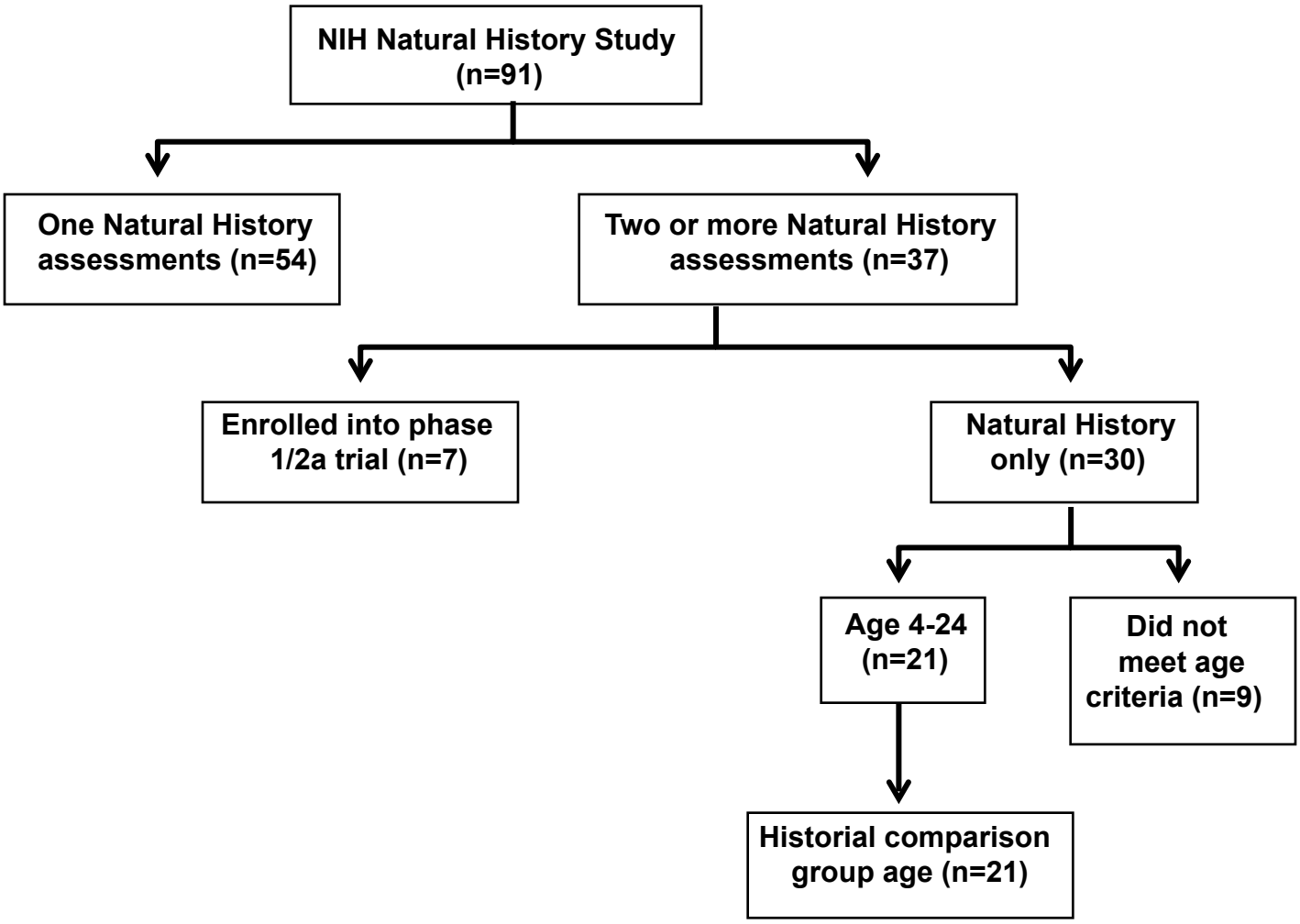
Appendix Figure 2. Individual Subject Dosing.

	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	50mg	200mg	200mg	200mg	300mg	300mg	300mg	300mg	300mg	300mg	300mg	300mg	300mg	600mg	600mg	600mg	900mg	900mg
	CDA102	Saline	50mg	50mg*	200mg	200mg	200mg	300mg	300mg	300mg	300mg	300mg	300mg	300mg	300mg	300mg	600mg	600mg	400mg	DI-2
	CDA103	Saline	50mg	200mg	200mg	200mg	300mg	300mg	300mg	300mg	300mg	300mg	300mg	300mg	300mg	600mg	600mg	900mg	900mg	900mg
Cohort 2	CDA104	Saline	200mg	200mg	200mg	300mg	300mg	300mg	300mg	300mg	300mg	300mg	300mg	300mg	600mg	600mg	600mg	900mg	900mg	600mg
	CDA105	Saline	200mg	200mg	200mg	200mg	300mg	300mg	300mg	300mg	300mg	300mg	300mg	300mg	600mg	DI-3		600mg	600mg	600mg
	CDA106	Saline	200mg	200mg	200mg	200mg	300mg	300mg	300mg	300mg	300mg	300mg	300mg	300mg	600mg	600mg	600mg	900mg	900mg	900mg
Cohort 3	CDA107	Saline	300mg	DI-1	200mg	200mg	200mg	200mg	200mg	200mg	200mg	200mg	200mg	200mg	300mg	300mg	300mg	400mg	400mg	400mg
	CDA108	Saline	300mg	DI-1	200mg	200mg	200mg	200mg	200mg	200mg	200mg	200mg	200mg	200mg	300mg	300mg	300mg	400mg	400mg	400mg
	CDA109	Saline	300mg	300mg	300mg	300mg	300mg	300mg	300mg	300mg	300mg	300mg	300mg	300mg	400mg	400mg	300mg	400mg	400mg	400mg
Cohort 4	CDA110	Saline	400mg	400mg	400mg	400mg	400mg	400mg	400mg	400mg	400mg	400mg	400mg	400mg	1200mg	1200mg	1200mg	1200mg	1200mg	1200mg
	CDA111	Saline	400mg	400mg	400mg	400mg	400mg	400mg	400mg	400mg	400mg	400mg	400mg	400mg	1200mg	1200mg	1200mg	1200mg	1200mg	DI-4
	CDA112	Saline	360mg*	400mg	400mg	400mg	400mg	400mg	400mg	400mg	400mg	400mg	400mg	400mg	1200mg	900mg	1200mg	1200mg	1200mg	1200mg
Cohort 5	CDA113	Saline	900mg	900mg	900mg	900mg	900mg	900mg	900mg	900mg	900mg	900mg	900mg	900mg						
	CDA114	Saline	900mg	900mg	900mg	900mg	900mg	900mg	900mg	900mg	900mg	900mg	900mg	900mg						
												50 mg	200 mg	300 mg	400 mg	600 mg	900 mg	1200 mg		

ND Dose Interuption DI-1 Ototoxiciy DI-3 Caretaker Hardship

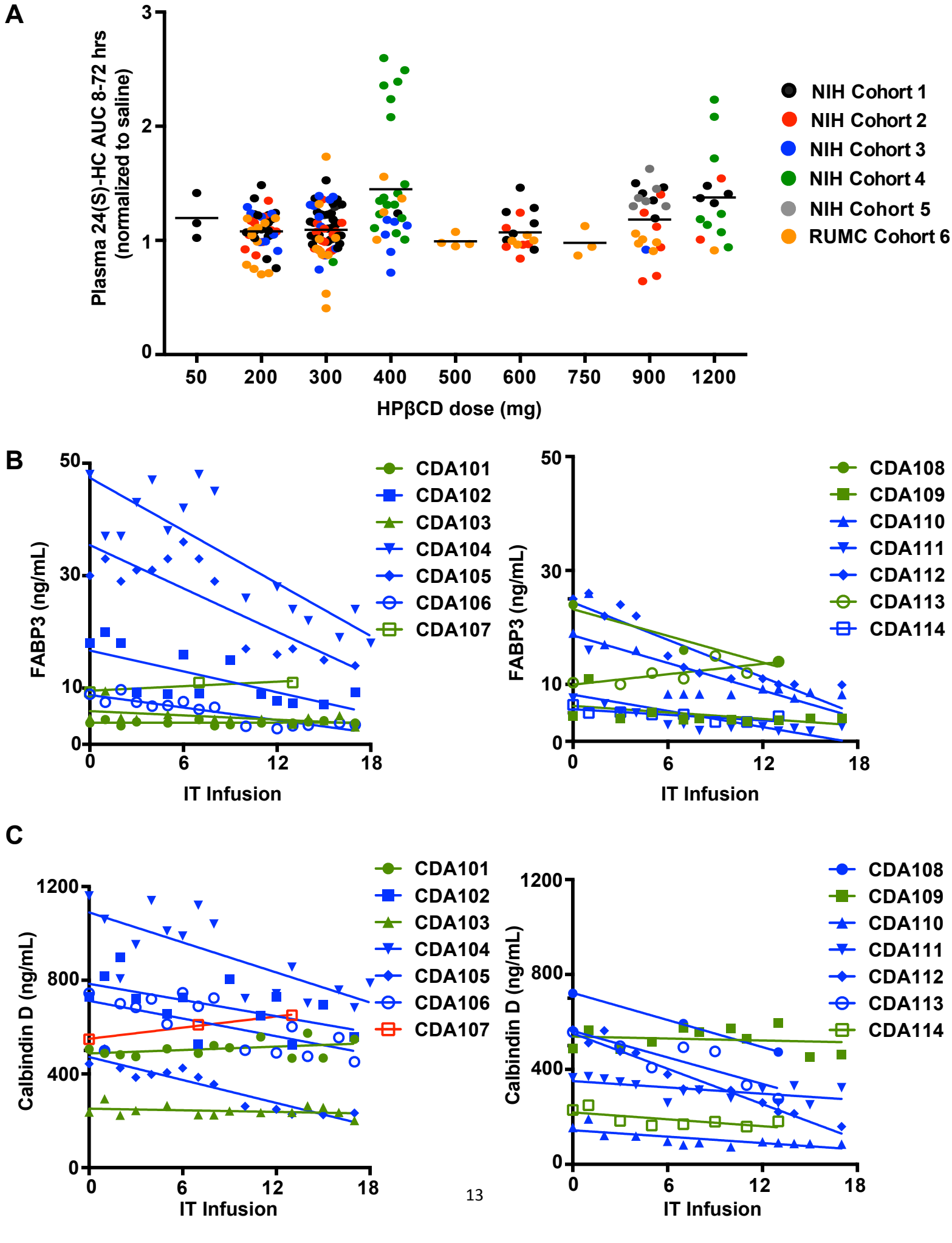
* Dosing error DI-2 Hepatocellular Carcinoma DI-4 Mastoiditis

Appendix Figure 3



Appendix figure 3. Consort diagram for selection of the Natural History Cohort.

Appendix Figure 4



Appendix figure 4. Biomarker data for individual participants. Plasma 24(S)-hydroxycholesterol (24(S)-HC) responses are shown for all HPβCD infusions. 24(S)-HC $AUC_{8\text{-}72hrs}$ values were normalized to the corresponding subject's 24(S)-HC $AUC_{8\text{-}72hrs}$ that was determined after infusion of saline (A). The NIH cohorts refer to the initial starting HPβCD dose. This was 50, 200, 300, 400 and 900 mg for NIH cohorts 1-5 respectively. The three RUMC participants are designated as cohort 6. Individual CSF FABP3 (B) and calbindin D (C) concentrations are plotted against the corresponding intrathecal infusions. Linear regressions of the FABP3 and calbindin D values are shown for individual participants. The data set for both FABP3 and calbindin D are presented in two panels for clarity. Significant negative regressions, non-significant regressions and significant positive regressions are shown in blue, green and red, respectively.

Appendix Figure 5

A

Natural History Individual Patient Data for NPC-CSS Domains

Subject ID	Ambulation	Fine Motor	Cognition	Swallow	Memory	Speech	Eye Movement	Hearing
NPC03	0	0	1	0	0	0	0	0
NPC04	1	1	0	0	0	0	0	0
NPC05	1	0	2	2	1	1	0	0
NPC07	2	0	0	1	0	0	0	0
NPC08	1	2	0	-2	2	0	0	0
NPC10	1	0	0	0	0	0	0	0
NPC12	0	0	0	1	0	0	1	0
NPC16	0	0	0	0	0	0	1	-1
NPC17	1	1	2	0	0	0	0	1
NPC23	0	0	0	0	0	0	0	0
NPC24	0	0	0	0	0	0	2	0
NPC28	0	0	0	0	1	1	1	0
NPC34	0	0	0	0	0	1	0	0
NPC40	0	0	0	0	0	0	0	0
NPC43	0	0	0	1	0	0	0	0
NPC44	0	1	1	0	0	0	0	0
NPC52	1	0	0	0	1	0	1	0
NPC54	0	1	1	0	0	0	0	0
NPC56	0	1	0	0	0	0	0	0
NPC64	0	0	0	0	0	2	0	0
NPC65	0	0	3	0	0	0	0	0

B

HPβCD Individual Pateint Data for NPC-CSS Domains

Subject ID	Ambulation	Fine Motor	Cognition	Swallow	Memory	Speech	Eye Movement	Hearing
CDA101	0	0	0	0	0	0	0	0
CDA102	0	0	0	0	-1	-1	1	0
CDA103	0	0	0	0	0	0	-1	0
CDA104	0	0	0	-1	1	0	1	1
CDA105	1	1	0	1	0	0	2	0
CDA106	0	0	0	0	0	-1	0	0
CDA107	0	2	0	1	0	0	0	0
CDA108	1	0	0	1	0	0	0	1
CDA109	0	0	0	0	0	0	0	2
CDA110	0	0	0	3	0	0	0	0
CDA111	0	0	0	-1	0	0	0	1
CDA112	0	1	-1	0	1	0	0	2
CDA113	0	0	0	0	0	0	1	1
CDA114	0	0	0	0	0	0	-1	3

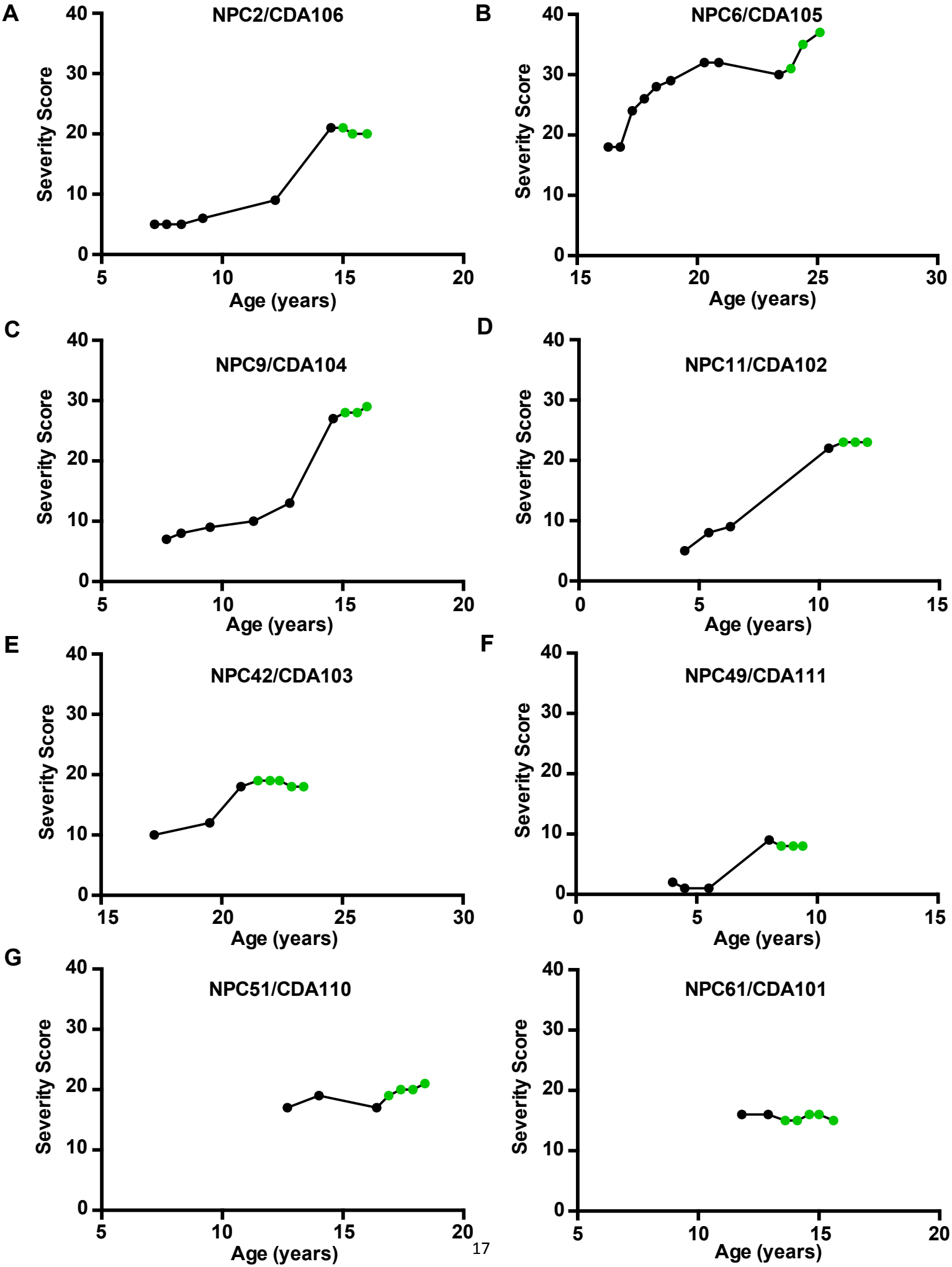
= Improvement (decline in score)

= Stable disease (no change in score)

= Worsening (increase in score)

Appendix figure 5. Heat maps of disease progression data for individual participants and NSS domains. (A) Heat map for 21 Natural History participants. (B) Heat map for 14 NIH HPβCD-treated patients. Numbers indicate the change in the domain score. Box shading indicates improvement (green), stable disease status (yellow), and sign/symptom progression (red).

Appendix Figure 6



Appendix figure 6. Plots of NSS minus hearing scores for individual participants. Eight participants in the NIH HPβCD trial had previously been evaluated at least once in the NIH Natural History study prior to the baseline visit for the HPβCD trial. Spaghetti plots of the NSS versus age are provided for these eight participants. Points in black indicate values obtained either at baseline or prior to enrollment in the HPβCD trial. Points in green indicate NSS values at six month intervals while receiving monthly intrathecal HPβCD infusions. When available, 24- and 30-month data were included.