Clinical Update on Intrathecal VTS-270 for the Treatment of Niemann-Pick Disease

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Michael, Marcia, and Christa Parseghian Scientific Conference for Niemann-Pick Type C Research
June 1-4, 2019

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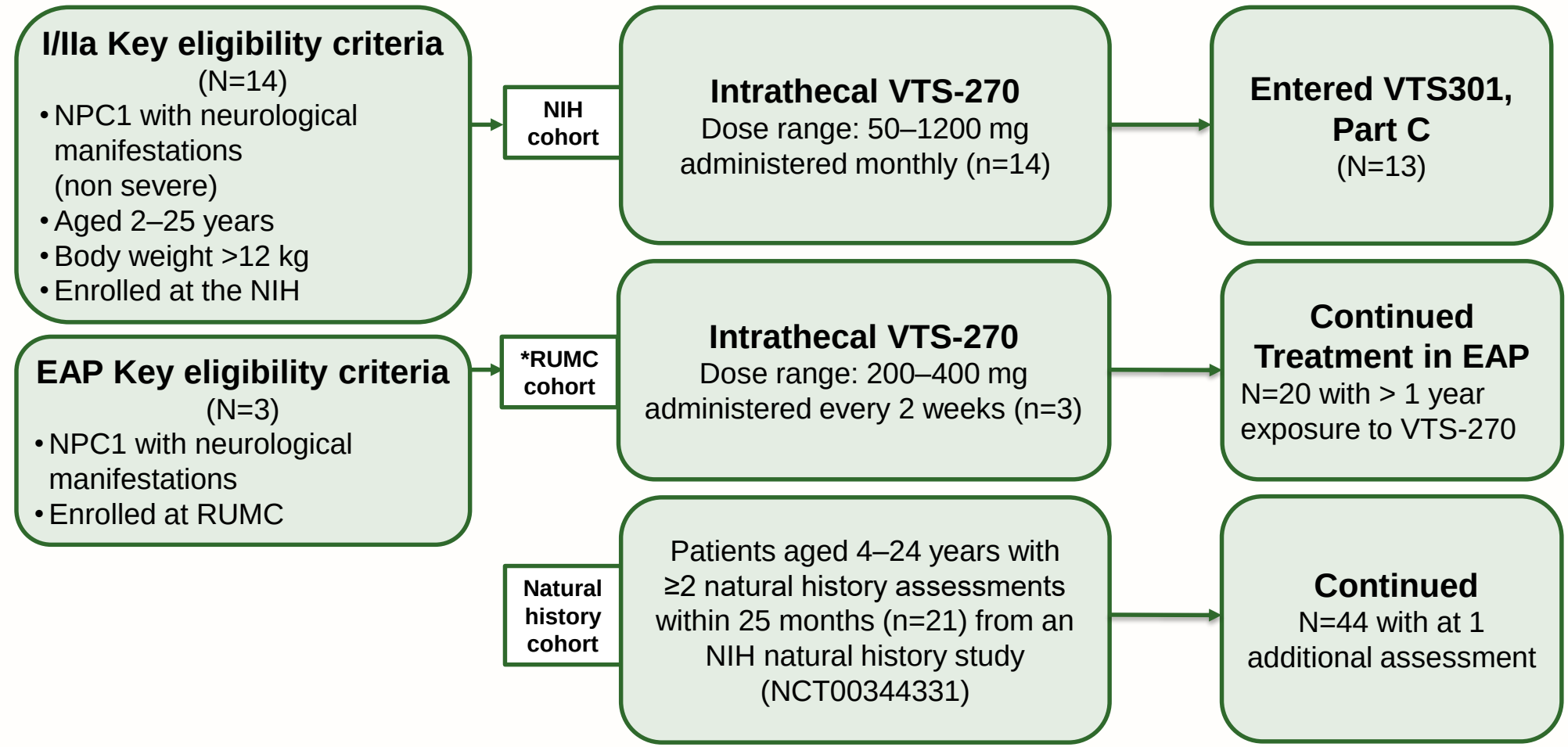
Mallinckrodt Pharmaceuticals Data Presented at Annual Scientific Conference

- **Michael, Marcia, and Christa Parseghian Scientific Conference for Niemann-Pick Type C (NPC) Research** Tucson, Ariz. - June 1-4, 2019 - presented Monday, June 3, 2019, 1:20-2:40pm Pacific.

- **Rationale for Mallinckrodt data presentation**: The data is being presented as the conference is a unique opportunity to engage the NPC scientific and patient community and discuss the results of the VTS-270 Phase 2B/3 clinical trial, along with other data, with the patients and parents that have supported the trial. While the company has communicated that the Phase 2B/3 trial top-line results did not meet statistical significance, this was an opportunity to share additional information more broadly as Mallinckrodt assesses the next steps for the overall VTS-270 program.

- **About the Conference:** This conference is about sharing basic, translational, and clinical research towards a greater understanding and a cure for Niemann-Pick Type C disease. Attendees include scientists, patients and patient advocates. For more information visit their website.

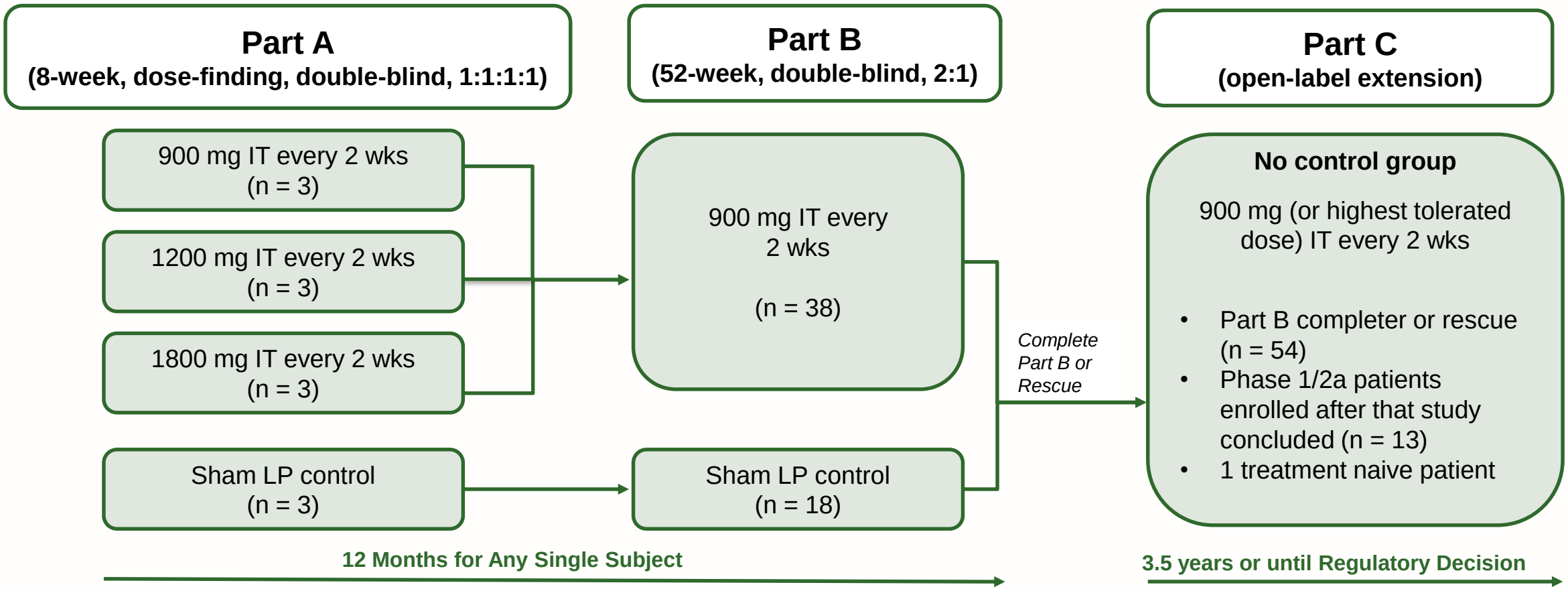
IT administration of VTS-270 was investigated in an open-label, dose-escalation phase I/IIa study



*Rush University Medical Center

Ory DS, et al. *Lancet*. 2017

VTS301: Prospective, randomized, double-blind, sham-controlled trial of adrabetadex in patients with neurological manifestations of NPC type 1 disease



Assessments: Safety, NPC Clinical Severity Scale (NPC-SS), Clinician Global Impression of Change (CGIC), Quality-of-Life

IT, intrathecal; LP, lumbar puncture; NPC, Neimann-Pick Type C.
https://clinicaltrials.gov/ct2/show/study/NCT02534844.

VTS301: Co-primary end points for Parts A/B agreed with FDA

Co-Primary End Points

- Change from baseline in NPC-SS composite at Week 52
- Blinded clinician CGIC at Week 52

Key Secondary End Points

- Proportion of clinician CGIC responders at Week 52
- Change from baseline in NPC-SS total score (less hearing/ABR) at Week 52
- Proportion of NPC-SS total score (less hearing/ABR) responders at Week 52

Other Secondary End Points

- Timed up and Go (TUG)
- 9-hole peg
- Caregiver CGIC
- EQ-5D-3L (quality of life measure)

ABR, auditory brain response; CGIG, clinician global impression of change; EQ-5D-3L, EuroQual 5-dimension 3-level scale; NPC-SS, NPC clinical severity scale.
https://clinicaltrials.gov/ct2/show/study/NCT02534844.

VTS301: Demographic and baseline characteristics (Part A/B; mITT population)

	Overall Treatment (N = 38)	Overall Sham (N = 18)	Total (N = 56)
Age (yrs), mean (SD)	12.7 (5.64)	11.7 (5.10)	12.4 (5.45)
Male, n (%)	22 (57.9%)	8 (44.4%)	30 (53.6%)
Weight (kg), mean (SD)	48.1 (25.27)	40.2 (18.98)	45.5 (23.51)
Miglustat use, n (%)	25 (65.8%)	9 (50.0%)	34 (60.7%)
NPC-SS category, n (%) 10-19 ≥ 20	 17 (44.7%) 12 (31.6%)	 9 (50.0%) 6 (33.3%)	 26 (46.4%) 18 (32.1%)
Seizures, n (%)	15 (39.5%)	5 (27.8%)	20 (35.7%)
Duration neuro symptoms (yr), mean (SD)	7.1 (4.15)	5.9 (5.16)	6.7 (4.5)
Baseline NPC-SS total score (minus hearing/ABR), mean (SD)	17.8 (6.48)	16.9 (8.16)	17.5 (7.01)

ABR, auditory brain response; mITT, modified intention to treat; NPC-SS, NPC clinical severity scale; SD, standard deviation.
Data on file.

VTS301: Disposition (Part A/B; mITT population)

- 56 patients randomized
  - 38 patients to adrabetadex
  - 18 patients to sham
- 49 patients completed Part A/B
  - 4 patients qualified for rescue option at Week 26—2 in each group
  - 3 patients early terminated Part A/B; additional subject completed Week 52 but did not enter Part C (returned to home country)
- 15 patients removed from Per-Protocol population (>20% doses missed, efficacy assessment error, caregiver/patient unblinded)
- 8 patients with dose reduction for tolerability (1 subject with dose reduction in both Part A and Part B for tolerability)
  - Part A—4 dose reductions (no subject tolerated 1800-mg dose)
  - Part B—5 dose reductions

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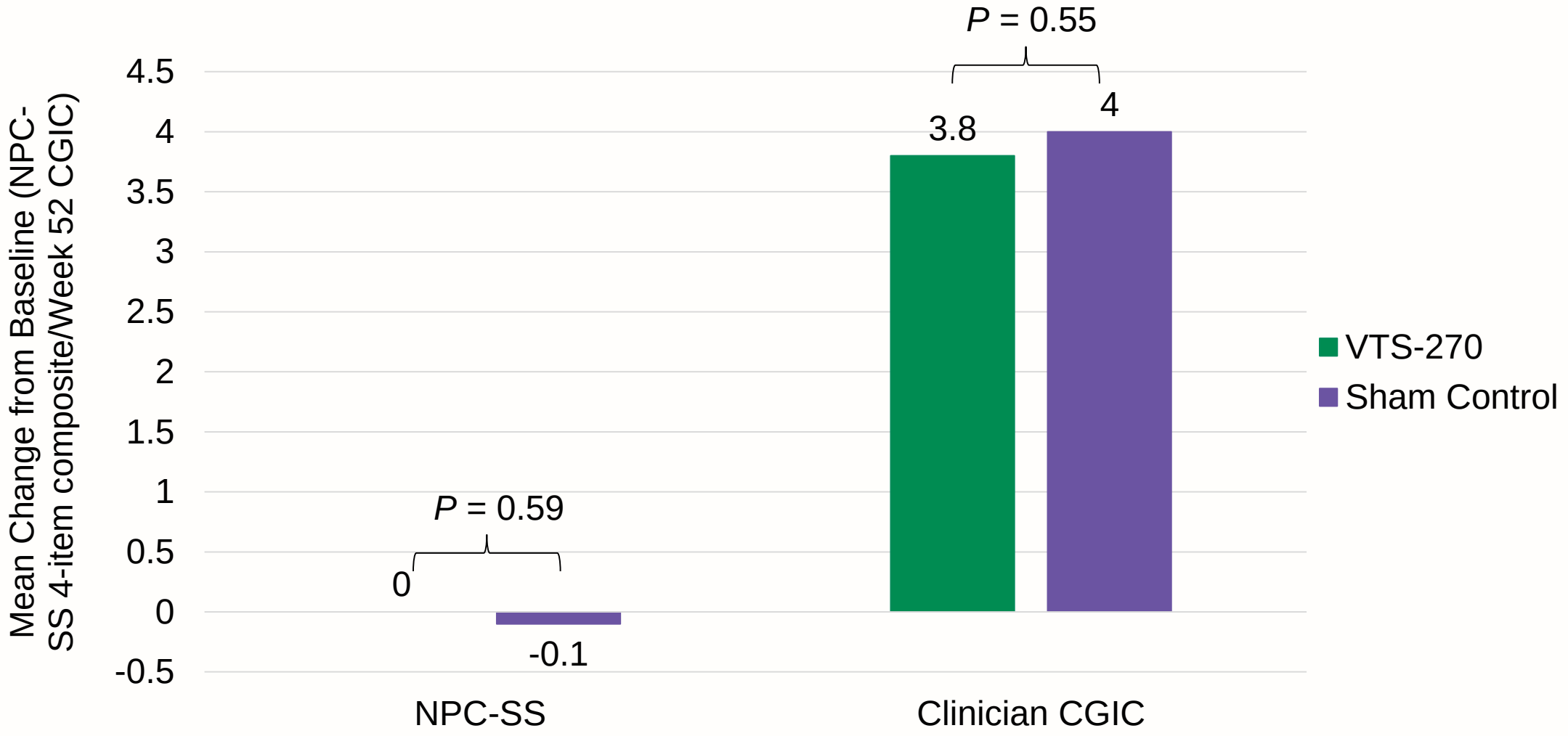
VTS301: Change from baseline in NPC-SS 4-item composite score at Week 52 and Clinician GCIC at Week 52 not significant



CGIG, clinician global impression of change; NPC-SS, NPC clinical severity scale
Data on file.

VTS301: Additional efficacy end points—No significant difference between adrabetadex and sham (Part A/B mITT population)

- No significant difference between patients treated with adrabetadex and sham patients on any efficacy measure (NPC-SS [all analyses], Clinician CGIC, Caregiver CGIC, TUG, 9-hole peg)

- Additional prospective analyses not significant, show same lack of separation between adrabetadex and sham

  - Per-Protocol population, dose (elimination of 1200 mg/1800 mg patients), site (elimination of non-compliant site)
  - Subgroup analyses (miglustat use, baseline NPC-SS total score, duration neurologic symptoms)

CGIG, clinician global impression of change; mITT, modified intention to treat; NPC-SS, NPC clinical severity scale
Data on file.

VTS301

Safety

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VTS301: Summary of safety (Part A/B, safety population)

- 55 patients experienced treatment-emergent adverse events (TEAEs)—38 (100%) patients treated with adrabetadex, 17 (94.4%) patients receiving sham
  - Dose interruption in 15 (39.5%) patients treated with adrabetadex, 2 (11.1%) patients receiving sham

- Most common TEAEs in adrabetadex group:

Preferred Term	Number (percentage) of patients
Vomiting	21 (55.3%) adrabetadex, 2 (11.1%) sham
Back pain	19 (50.0%) adrabetadex, 3 (16.7%) sham
Fatigue	18 (47.4%) adrabetadex, 3 (16.7%) sham
Gait disturbance	16 (42.1%) adrabetadex, 2 (11.1%) sham
Hearing impaired	15 (39.5%) adrabetadex, 6 (33.3%) sham
Hypoacusis	14 (36.8%), 0 sham
Diarrhea	14 (36.8%) adrabetadex, 1 (5.6%) sham
Pyrexia	14 (36.8%) adrabetadex, 3 (16.7%) sham

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VTS301: Summary of safety, TEAE severity (Part A/B, safety population)—differential between adrabetadex and sham is driven by hearing impairment events

- 33 patients (86.8%) in the adrabetadex group and 5 patients (27.8%) in the sham group experienced TEAEs with a Common Terminology Criteria for Adverse Events (CTCAE) grade of ≥3
  - Events in more than 1 patient include:

Adrabetadex, n (%)		Sham, n (%)	
Hearing impaired	13 (34.2)	Epilepsy	3 (16.7)
Hypoacusis	7 (18.4)		
Deafness	5 (13.2)		
Ataxia	4 (10.5)		
Dysphagia; Dysarthria; Pneumonia aspiration	3 (7.9) each		
Aspiration; Tinnitus; Vomiting; Gait disturbance; Fall; Musculoskeletal stiffness; Hypoxia; Aspiration	2 (5.3) each		

TEAE, treatment-emergent adverse event.
Data on file.

VTS301: Summary of safety, treatment-emergent SAEs (Part A/B, safety population)—most events expected due to underlying disease

- 24 patient experienced SAEs
  - No fatal events
  - Non-fatal events occurred in 20 (52.6%) patients receiving adrabetadex and 4 (22.2%) sham patients

- Treatment-emergent SAEs occurring in >1 patients receiving adrabetadex were:

Preferred Term	**n (%)**
Hearing impaired	4 (10.5) adrabetadex, 1 (5.6) sham
Pneumonia, aspiration	4 (10.5) adrabetadex, 1 (5.6) sham
Deafness	3 (7.9) adrabetadex, 0 sham
Seizure	3 (7.9) adrabetadex, 1 (5.6) sham
Dysphagia	2 (5.3) adrabetadex, 1 (5.6) sham
Aspiration	2 (5.3) adrabetadex, 1 (5.6) sham

SAE, serious adverse event.
Data on file.

Phase 2b/3 parts A/B: safety summary

- Safety findings were consistent with the safety profile in phase 1/2 study
- Further work is required to understand potential impact of adrabetadex on hearing

Presentations and Discussion:

Longitudinal NPC-SS Data—Determining Clinical Meaningfulness

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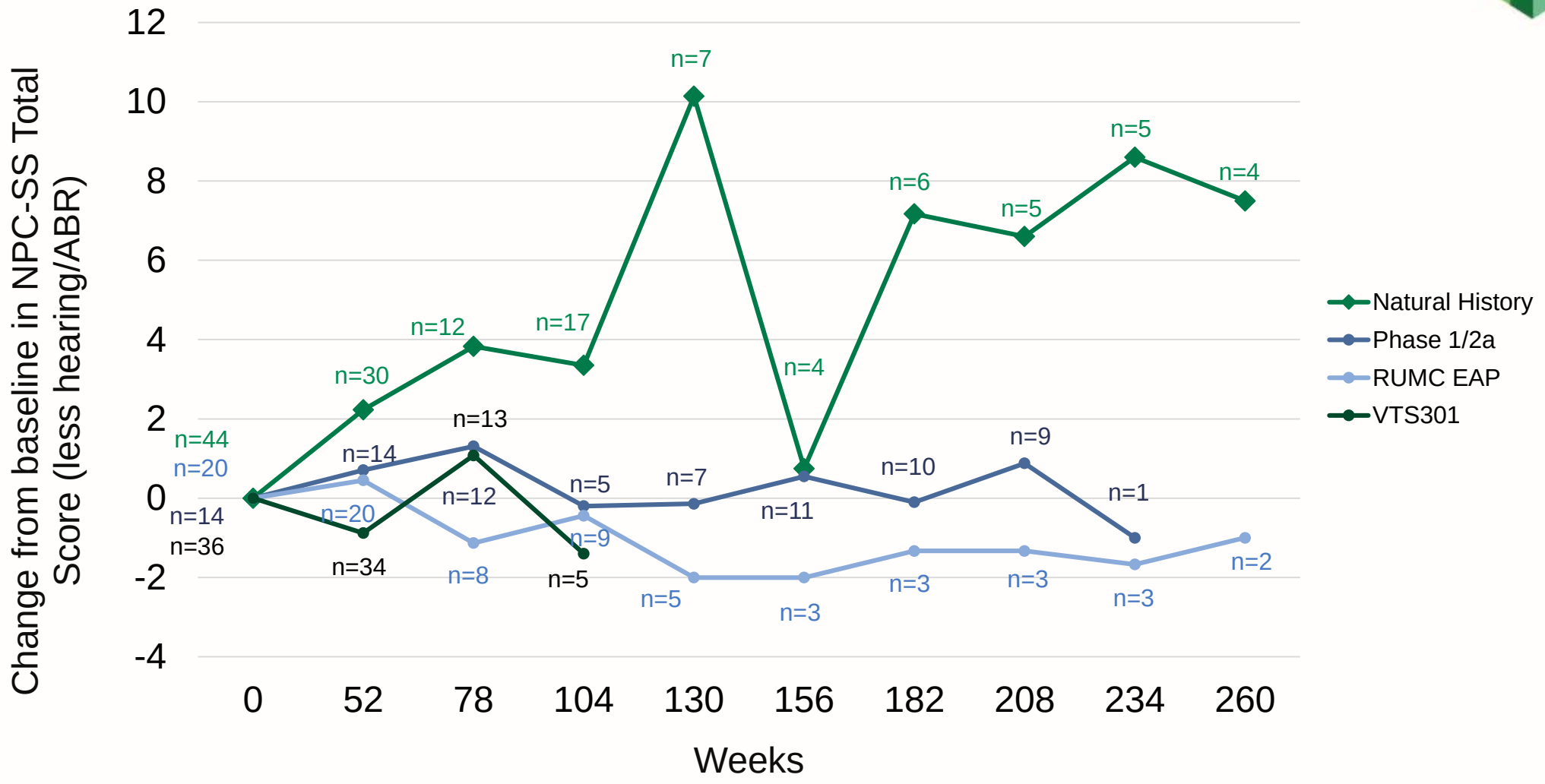
Longitudinal analyses—preliminary evaluation of open-label data from 3 cohorts treated with adrabetadex

- Available treated patients (n = 71)—exposed to adrabetadex for at least 52 weeks
  - 13-CH-0001—14 patients
  - VTS301—37 patients (includes sham patients with ≥ 52 weeks treatment with adrabetadex; no imputation)
  - RUMC EAP—20 patients
- Natural history cohort (n = 44)—patients with at least 1 year of participation who remain off investigational treatment

Evaluation of longitudinal data from multiple adrabetadex treated cohorts and untreated natural history cohort



PRELIMINARY UNCONTROLLED DATA—informal data snapshot Dec 2018; requires confirmation

Data on file.

Overall summary

- Efficacy
  - No statistically significant difference between the sham group and the treatment group on the co-primary end points at Week 52
  - Longitudinal evaluation of treated patients in VTS301 shows similar trend to other treated patients from phase 1/2a and RUMC EAP—lack of statistical comparisons preclude a determination of a treatment effect
- Safety
  - VTS-301 safety results are generally in line with the safety profile established in phase 1/2a trials and from clinical experience
  - Hearing impairment, an identified risk for IT use of adrabetadex, was noted as a TEAE

AE, adverse event; IT, intrathecal; TEAE, treatment-emergent adverse event.

Acknowledgements

- NIH NPC Natural History Trial
  - Denny Porter (PI) and Nicole Farhat
- Phase I/IIa VTS-270 trial
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- Rush University Medical Center Expanded Access Protocol
  - Liz Berry-Kravis (PI)
- Phase IIb/III VTS-270 trial
  - Denny Porter and Liz Berry-Kravis (co-PIs) and the site principal investigators: Elizabeth Berry-Kravis, Olaf Bodamer, Miereia Del Toro Riera, Leon Dure, Fatih Ezgu, Michael Fahey, Can Ficicioglu, Renata Gallagher, James Gibson, Paul Gissen, Coy Heldermon, Julia Hennermann, Bénédicte Heron, Mary Kay Koenig, Paul Levy, Thomas Lücke, Thorsten Marquardt, Sameh Morkous, Denny Porter, Michael Raff, Tyler Reimschisel, Janet Thomas, Meral Topcu, Suresh Vijay, Mark Walterfang, Raymond Wang
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