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

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Mallinckrodt Pharmaceuticals

Michael, Marcia, and Christa Parseghian Scientific Conference for Niemann-Pick Type C Research
June 1-4, 2019
Mallinckrodt Pharmaceuticals Data Presented at Annual Scientific Conference


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

**I/IIa Key eligibility criteria**
(N=14)
- NPC1 with neurological manifestations (non severe)
- Aged 2–25 years
- Body weight >12 kg
- Enrolled at the NIH

**EAP Key eligibility criteria**
(N=3)
- NPC1 with neurological manifestations
- Enrolled at RUMC

**Intrathecal VTS-270**
Dose range: 50–1200 mg administered monthly (n=14)

Entered VTS301, Part C (N=13)

**Intrathecal VTS-270**
Dose range: 200–400 mg administered every 2 weeks (n=3)

Continued Treatment in EAP
N=20 with > 1 year exposure to VTS-270

Patients aged 4–24 years with ≥2 natural history assessments within 25 months (n=21) from an NIH natural history study (NCT00344331)

Continued
N=44 with at 1 additional assessment

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

Part A
(8-week, dose-finding, double-blind, 1:1:1:1)

- 900 mg IT every 2 wks (n = 3)
- 1200 mg IT every 2 wks (n = 3)
- 1800 mg IT every 2 wks (n = 3)
- Sham LP control (n = 3)

Part B
(52-week, double-blind, 2:1)

- 900 mg IT every 2 wks (n = 38)
- Sham LP control (n = 18)

Part C
(open-label extension)

- Sham LP control (n = 3)

No control group
900 mg (or highest tolerated dose) IT every 2 wks

- Complete Part B or Rescue
- Part B completer or rescue (n = 54)
- Phase 1/2a patients enrolled after that study concluded (n = 13)
- 1 treatment naive patient

3.5 years or until Regulatory Decision

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

IT, intrathecal; LP, lumbar puncture; NPC, Niemann-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; CGIC, clinician global impression of change; EQ-5D-3L, EuroQual 5-dimension 3-level scale; NPC-SS, NPC clinical severity scale.
VTS301: Demographic and baseline characteristics (Part A/B; mITT population)

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

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

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

Mean Change from Baseline (NPC-SS 4-item composite/Week 52 CGIC)

- P = 0.59
- P = 0.55

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)
VTS301

Safety
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:

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Adrabetadex, n (%)</th>
<th>Sham, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hearing impaired</td>
<td>13 (34.2)</td>
<td>3 (16.7)</td>
</tr>
<tr>
<td>Hypoacusis</td>
<td>7 (18.4)</td>
<td></td>
</tr>
<tr>
<td>Deafness</td>
<td>5 (13.2)</td>
<td></td>
</tr>
<tr>
<td>Ataxia</td>
<td>4 (10.5)</td>
<td></td>
</tr>
<tr>
<td>Dysphagia; Dysarthria; Pneumonia aspiration</td>
<td>3 (7.9) each</td>
<td></td>
</tr>
<tr>
<td>Aspiration; Tinnitus; Vomiting; Gait disturbance; Fall; Musculoskeletal stiffness; Hypoxia; Aspiration</td>
<td>2 (5.3) each</td>
<td></td>
</tr>
</tbody>
</table>

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:

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hearing impaired</td>
<td>4 (10.5) adrabetadex, 1 (5.6) sham</td>
</tr>
<tr>
<td>Pneumonia, aspiration</td>
<td>4 (10.5) adrabetadex, 1 (5.6) sham</td>
</tr>
<tr>
<td>Deafness</td>
<td>3 (7.9) adrabetadex, 0 sham</td>
</tr>
<tr>
<td>Seizure</td>
<td>3 (7.9) adrabetadex, 1 (5.6) sham</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>2 (5.3) adrabetadex, 1 (5.6) sham</td>
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<tr>
<td>Aspiration</td>
<td>2 (5.3) adrabetadex, 1 (5.6) sham</td>
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</table>
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
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
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**
  - Denny Porter (PI), Dan Ory (co-PI), Nicole Farhat, Liz Ottinger, Steve Walkley, Charles Vite, Cristin Davidson and the TRND team

- **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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