



Cognitive Vitality Reports[®] are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Hydroxypropyl- β -cyclodextrin

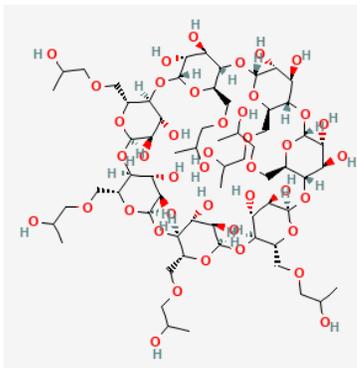
Evidence Summary

HP β CD slows disease progression in Niemann-Pick disease Type C1. Adverse events depend on route, dose, and dosing regimen, but ototoxicity and increased liver enzymes are frequently observed.

Neuroprotective Benefit: HP β CD slows disease progression in Niemann-Pick disease by facilitating movement of cholesterol from lysosomes to other parts of the cell. It remains to be seen whether HP β CD would have neuroprotective benefits in AD.

Aging and related health concerns: HP β CD has shown benefits in rodent models of stroke, hypoxia-ischemia, and atherosclerosis, but there have not been any studies in humans.

Safety: Adverse events depend on route, dose, and dosing regimen, plus there are individual differences. Ototoxicity, tinnitus, fatigue, and increased liver enzymes are frequently observed.

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| <p>Availability: under clinical development; research-grade is available</p> | <p>Dose: In a phase 2b/3 trial in NPC1, VTS-270 will be administered every 2 weeks via lumbar intrathecal infusion at a dose of 900-1800 mg (NCT02534844). In a phase 3 trial in NPC1, Trappsol® Cyclo™ will be administered intravenously at 2000 mg/kg (CycloTherapeutics.com).</p> | <p>Chemical formula: ranges, depending on the number of hydroxypropyl groups, e.g., $C_{63}H_{112}O_{42}$</p> <p>MW: ranges, e.g., 1541.5</p>  <p>Source: PubChem</p> |
| <p>Half life: 6-10 hours, but may depend on formulation</p> | <p>BBB: penetrant, but may depend on formulation</p> | |
| <p>Clinical trials: There are numerous trials where HPβCD is used as an excipient of a drug, including thousands of people (e.g., Phase 3 trials testing HPβCD-diclofenac in postoperative pain). The Niemann-Pick disease trials have been small, ranging from 3 to 14 subjects due to the rare disease designation.</p> | <p>Observational studies: none</p> | |

What is it? Hydroxypropyl-β-cyclodextrin (HPβCD) is a cyclic oligosaccharide best known for its use as an excipient. It consists of 7 glucopyranose units, with a hydrophilic exterior and a hydrophobic interior, allowing it to form water-soluble inclusion complexes with hydrophobic molecules, increasing the solubility and bioavailability of many drug compounds ([Brewster and Loftsson, 2007](#)). As an independent drug/chemical, it has been most studied as a potential therapeutic for Niemann-Pick disease, Type C1 (NPC1), an autosomal recessive lysosomal storage disorder due to mutations of NPC1 or NPC2 and characterized by endolysosomal accumulation of unesterified cholesterol and progressive neurodegeneration, leading to mortality generally 10-15 years after symptom onset. HPβCD can take the place of mutated NPC1 or NPC2 protein to facilitate movement of stored cholesterol from the late endosomal/lysosomal system to other parts of the cell, so cholesterol can be further processed and excreted from the cell ([Liu et al., 2009](#)).

VTS-270 (Adrabetadex) and Trappsol[®] Cyclo[™] ([Cyclo Therapeutics](#)) are HP β CD therapeutics under clinical development as novel treatments for NPC1. VTS-270 was originally under development by Vtesse, then Sucampo acquired Vtesse, then Mallinckrodt Pharmaceuticals acquired Sucampo. In July 2021, Mandos acquired VTS-270 (Adrabetadex) from Mallinckrodt Pharmaceuticals. VTS-270 received Breakthrough Therapy designation status by the FDA for the treatment of NPC1 and is currently undergoing a phase 2b/3 clinical trial ([PRNewswire.com](#)). Trappsol[®] Cyclo[™] is under development for the treatment of both NPC1 and Alzheimer's disease by Cyclo Therapeutics, Inc. ([CycloTherapeutics.com](#)).

It is worth noting that while VTS-270 and Trappsol[®] Cyclo[™] are both HP β CD therapeutics, they are not chemically equivalent. HP β CDs are synthesized by condensation between β -cyclodextrin (β CD) and propylene oxide. This process does not lead to a single molecular HP β CD species but rather to a complex mixture of HP β CD species with differing degrees of substitution (hydroxypropylation) ([Yergey et al., 2017](#)). In this regard, Trappsol[®] Cyclo[™] has significantly greater numbers of hydroxypropyl groups than VTS-270. In addition, doubly-charged heterodimers are more prevalent in Trappsol[®] Cyclo[™] than VTS-270. The proportion of nonspecific chemical noise was greater with Trappsol[®] Cyclo[™] than VTS-270, consistent with previous findings that HP β CDs with higher hydroxypropylation have more contaminants.

*This report focuses on HP β CD as a stand-alone therapeutic and does not discuss in detail the studies where HP β CD is used as an excipient.

Neuroprotective Benefit: HP β CD slows disease progression in Niemann-Pick disease by facilitating movement of cholesterol from lysosomes to other parts of the cell. It remains to be seen whether HP β CD would have neuroprotective benefits in AD.

Types of evidence:

- 2 double-blind, randomized, parallel group, uncontrolled clinical trial in Niemann-Pick disease
- 2 open-label randomized clinical trials in Niemann-Pick disease
- 1 open-label non-randomized dose-escalation study in Niemann-Pick disease
- 2 open-label, long-term clinical study in Niemann-Pick disease
- 1 case study in Niemann-Pick disease
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

No studies have tested HP β CD for the prevention of dementia or age-related cognitive decline in people.

Human research to suggest benefits to patients with dementia:

No studies have tested HP β CD in patients with dementia. Cyclo Therapeutics' Trappsol[®] Cyclo[™] has received IND clearance to advance to a phase 2 study in Alzheimer's disease (CycloTherapeutics.com).

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

The majority of clinical studies testing HP β CD have tested VTS-270 and Trappsol[®] Cyclo[™], and they have all been in NPC1. A few laboratory studies have investigated the effects of HP β CD in Alzheimer's models.

VTS-270 in NPC1 patients: Numerous studies have evaluated the efficacy of VTS-270 in NPC1 patients.

In a phase I/II, open-label, non-randomized, dose-escalation trial in 14 NPC1 patients, monthly intrathecal treatment of VTS-270 (initial doses of 50, 200, 300, 400, or 900 mg per month, dose-escalated to 600 or 1200 mg, as tolerated) for up to 18 months resulted in slowed disease progression and improved biomarkers suggesting improved neuronal cholesterol homeostasis and decreased neuronal pathology ([Ory et al., 2017](#)). The NPC Neurological Severity Scores (NNSS) for the 14 participants treated monthly increased (worsened) at a rate of 1.22 ± 0.34 points per year compared with 2.92 ± 0.27 points per year ($p=0.0002$) for the 21-patient historical comparison group. Decreased progression was observed for NNSS domains of ambulation ($p=0.0622$), cognition ($p=0.0040$) and speech ($p=0.0423$). Only the hearing domain showed a notable worsening with VTS-270 ($p=0.0518$). When the hearing-related components were removed from analysis, VTS-270 treatment showed a progression rate of 0.69 ± 0.34 points per year versus 2.67 ± 0.27 points per year for the comparison group ($p<0.0001$). In 3 participants given 600-900 mg monthly of VTS-270, the cerebral spinal fluid (CSF) levels of 24(S)-hydroxycholesterol, the target engagement biomarker, doubled 72 hours after drug administration, suggesting improved neuronal cholesterol homeostasis. CSF levels of calbindin D and FABP3, biomarkers of neuronal damage, decreased significantly in the majority of VTS-270-treated patients.

In an open-label extension of the study described above, the 14 NPC1 patients treated with VTS-270 were followed for up to 36 months ([Farmer et al., 2019](#)). The treatment showed slowing of disease progress, consistent with the initial study above. There were no meaningful declines in IQ scores or standard scores and age equivalents of adaptive functioning. Adaptive behavior, measured by the



Vineland-II Adaptive Behavior Composite standard score, decreased by 1.76 points per year, which were not due to worsening, as age-equivalent annualized slopes for communication, socialization, daily living skills, and motor skills were positive, indicating slower-than-average acquisition of skills. Immediate memory, recall, and recognition were evaluated with the Wide Range Assessment of Memory and Learning – Second Edition, and although the small sample size prohibited statistical analysis, patients showed negligible change after 36 months of treatment. Caveats from these studies include the small sample size, the lack of a contemporaneous control group, and the inability to establish a dose-response relationship to neuropsychological outcomes due to the dose-escalation design.

In an open-label, long-term clinical study as part of an investigational new drug application for expanded access (IND 119856), 3 patients with NPC1 received intrathecal treatment (via lumbar puncture) of VTS-270 (dosing based on tolerability, from 200-1200 mg, every 2 weeks) for 2.5-3 years, and showed overall stable disease or mild improvement ([Berry-Kravis et al., 2018](#)). No worsening in any domain except eye movements (vertical pursuit gain) was observed, and in other domains, improvement in scores on measures were seen over time for one or more patients. Patient 1 showed improvement in expressive language and had increased spontaneous language, was reading short sentences, singing and laughing again, and carried out directions faster. Patient 2 showed improvements in IQ score (WISC-5/WAIS-4), core language score (measured by CELF-4), and general memory scores (measured by WRAML-2), with stable to improved scores on executive function (measured by D-KEFS). Patient 2 had stable school performance and graduated high school with a regular curriculum and some accommodations and continued onto a community college program. Patient 3 showed gradual improvement in IQ score (WAIS-4), with stable performance for the core language (CELF-4), general memory (WRAML-2), and executive function (D-KEFS). Patient 3 had stable performance in a community college and subsequent job training program and carried out office work well. Her gait had become steadier, and she had become less prone to falling. Fine motor and drawing skills were improved. The NIH Toolbox Cognitive Battery scores were essentially stable for Patient 2 and 3, with an increase in the Pattern Comparison Processing Speed subscore in Patient 2. Overall, the Niemann-Pick disease type C (NPC) Neurological Severity Scale (NSS) showed stable to slightly improved ratings. Due to the progressive nature of NPC1, the observed trajectories suggest that intrathecal VTS-270 has stabilized the disease over an extended period of time.

In a phase I/II, non-randomized, open-label clinical trial in 3 infants with NPC1, intravenous VTS-270 treatment (500 to 1000 mg/kg at a rate of 250 mg/kg/hour) through a peripherally inserted central catheter, twice a week for 6 weeks followed by monthly infusions for 6 months resulted in reduced liver enzymes (AST and ALT) and reduced bile acid marker (3 β ,5 α ,6 β -trihydroxy-cholan-24-oyl glycine; TCG),

generated from cholesterol sequestered in lysosome, though these biomarkers remained elevated ([Reynolds et al., 2021](#)). A fourth patient received intravenous VTS-270 under an emergency investigational new drug study but later passed away from her underlying condition (end stage liver disease) that was unrelated to drug administration.

Trappsol® Cyclo™ in NPC1 patients: In a phase I/II randomized double-blind, parallel group study with no control group, intravenous infusion of Trappsol® Cyclo™ at doses of 1500 mg/kg (n=5), 2000 mg/kg (n=4), and 2500 mg/kg (n=3) (over 8-9 hours every 2 weeks) for a 48-week period were tested in patients with NPC1 ([presentation](#) from Australian NPC Disease Foundation Annual Conference, June 25, 2021). Trappsol® Cyclo™ reduced tau in the cerebrospinal fluid (CSF) of NPC patients and led to a decrease in a plasma biomarker, lysosphingomyelin-509, demonstrating that it is clearing lipids from cells. Based on ultrasound data, there was a trend in reduction of hepatosplenomegaly (mean liver size reduced by 0.5 cm and mean spleen size reduced by 0.95 cm).

The efficacy outcome measure was at least a one-point reduction (improvement) in 2 or more of the 17-Domain NPC Clinical Severity Scale measure. Eight out of the 9 patients met this endpoint (89%). Cognition was improved by 2 points in 1 patient. Speech was improved by 1 point in 1 patient. Fine motor skills were improved by 1 point in 2 patients ([presentation](#) from Australian NPC Disease Foundation Annual Conference, June 25, 2021).

The second efficacy outcome measure was the Global Impression of Disease severity at 48 weeks. Using the Clinician's Global Impression of Improvement scale, 7 of 9 patients improved ([presentation](#) from Australian NPC Disease Foundation Annual Conference, June 25, 2021). One improved "very much", 1 was "much improved", 5 were "minimally improved", and 2 were "unchanged". None of the patients became "minimally worse", "much worse", or "very much worse". Because of the progressive nature of NPC, an improvement or stability of disease is considered a success.

In a phase 1, randomized, double-blind, parallel group study with no control group, intravenous infusion of Trappsol® Cyclo™ at doses of 1500 mg/kg (n=6) and 2500 mg/kg (n=4) (over 8-9 hours every 2 weeks) for a 14-week period were tested in 10 patients with NPC1 ([presentation](#) from Australian NPC Disease Foundation Annual Conference, June 25, 2021). Liver tissue filipin staining showed that Trappsol® Cyclo™ cleared cholesterol. After treatment, CSF tau levels were reduced in 6 out of 10 patients, remained stable in 2 patients, and increased in 2 patients. In a pharmacodynamics study, 24S-hydroxycholesterol, a cholesterol metabolite, was increased in serum after Trappsol® Cyclo™ treatment, demonstrating the drug's effect on CNS cholesterol metabolism.

Other/mixed HPβCD formulations in NPC1 patients: In an open-label long-term study, both VTS-270 and Trappsol® Cyclo™ were used in the treatment of 12 NPC1 patients ([Hastings et al., 2019](#)). The route of treatment varied with some people receiving intravenous doses while others receiving intrathecal treatment followed by intravenous treatment. Intravenous treatment lasted 17-92 months, followed by an addition of intrathecal treatment for 10-74 months in some patients. NPC1 patients with moderate disease showed slowing of disease progression with HPβCD. Severely affected NPC1 patients demonstrated periods of stability but eventually showed disease progression. Neurologic and neurocognitive benefits were seen in most patients with intravenous HPβCD alone, independent of whether they received intrathecal administration. In 2 patients, improvements were found in neurologic (fine and gross motor, swallowing), neurocognitive, and/or behavioral/psychiatric manifestations of the disease. Physicians and caregivers reported improvements in quality of life for the patients on intravenous therapy. Based on medical records, 8 out of 12 patients reported increased well-being attributable to increased ability to focus, increased alertness resulting in improved communication, less confusion, improved behavior, and better ability to manage activities of daily living. Improvements also included reduced hepatomegaly and decreased transaminase levels.

In a case study of 1 female patient (8 years old) with NPC1 gene mutations detected at 2 months of age, intrathecal HPβCD treatment (initially at a dose of 10 mg/kg, every other week and increased to 10 mg/kg twice a week) for 2 years resulted in stabilization of clinical symptoms and signs, with maintenance of residual neurological functions, and decreased CSF levels of total-tau ([Matsuo et al., 2014](#)). At 3 years of age, the patient started to exhibit rapid neurological deterioration, including progressive ataxia, cataplexy, dysarthria, dysphagia, and convulsions. She was started on intravenous HPβCD treatment at 4 years of age, at which point she had hepatosplenomegaly, was able to walk indoors with assistance, and spoke only a few unclear words. She also exhibited vertical gaze palsy, mild occasional dysphagia, slight hypotonia, ataxia, frequent attacks of cataplexy, and rare convulsions. After 1 year of treatment, the hepatosplenomegaly was slightly improved, but her neurological signs had worsened as she gradually developed dysphagia, rigidity, and frequent seizures, and consequently, became bed-ridden and unable to speak. Head MRI also showed progressive brain atrophy. After 2 years of intravenous HPβCD treatment, intrathecal HPβCD therapy was started at the age of 6 years and continued for 2 years. The dose was increased by up to 450 mg per week, and after 15 months, the treatment schedule was changed to 200 mg twice a week. The levels of CSF total tau gradually decreased after beginning intrathecal therapy, but when the dose was increased to 300 mg twice a week, there was a transient increase in CSF total tau, so the dose was reduced back to 200 mg twice a week. Intravenous HPβCD was stopped 12 months after the start of intrathecal treatment, while miglustat treatment (approved in the EU, Japan, and Canada for the treatment of NPC) continued.



Seizure frequency was unchanged with treatment. No significant changes were seen with brain MRI, but MRS imaging indicated decreased myelin destruction and an increase in N-acetylaspartate to creatine ratio, suggesting decreased neuronal and axonal damage. PET imaging indicated increased metabolism and activities in the brain. Swallowing function improved after 18 months of intrathecal treatment.

Laboratory studies testing HP β CD in rodent models of Alzheimer's disease: In a mouse model of Alzheimer's (TgCRND8 mice), intracerebroventricular Trappsol® Cyclo™ treatment (40 mg/kg/day) for 14 days markedly reduced the sizes of enlarged autolysosomes and lowered their content of GM2 ganglioside (a substrate for a lysosomal enzyme) and A β ([Yang et al., 2017](#)). However, Trappsol® Cyclo™ treatment did not alter brain amyloid plaque load, A β levels, or amyloid precursor protein processing. Trappsol® Cyclo™ treatment did not affect autophagy induction but stimulated lysosomal proteolytic function by increasing cathepsin D activity, levels of cathepsins B and D, and two proteins known to interact with cathepsin D, NPC1 and ABCA1. Trappsol® Cyclo™ also delayed autophagosome maturation and inhibited autophagosome-lysosome fusion. Slowing substrate delivery to lysosomes may relieve lysosomal stress due to accumulated substrates. However, prolonged or excessive interference with cellular membrane fusion/autophagosome maturation could be problematic. The delay in autophagosome maturation could be detrimental to cellular homeostasis due to the gradual build-up of autophagy substrates, which would be a concern for long-term treatment.

In rats where A β 42 was infused bilaterally into the hippocampus, intranasal administration of HP β CD polymeric microspheres (spray-dried mucoadhesive microspheres) for 7 days provided protection against apoptosis induced by A β 42, by decreasing Bax levels and increasing Bcl-2 levels, reducing oxidative stress, decreasing DNA fragmentation, and improving mitochondrial function ([Yalcin et al., 2016](#))

APOE4 interactions: Unknown.

Aging and related health concerns: HP β CD has shown benefits in rodent models of stroke, hypoxia-ischemia, and atherosclerosis, but there have not been any studies in humans.

Types of evidence:

- Several laboratory studies

No studies have tested HP β CD for the prevention or treatment of age-related diseases in humans. There are several laboratory studies that have examined the efficacy of HP β CD in rodent models.

In a mouse model of stroke (distal middle cerebral artery occlusion), treatment with HP β CD (4 g/kg, s.c.) 3 times per week for 6 weeks, starting 7 days after stroke surgery, aided in the restoration of lipid homeostasis, attenuated lipid droplet and immune cell accumulation, increased transcripts associated with neuronal function in peri-infarct regions, and improved recovery, both transcriptionally and functionally ([Becktel et al., 2022](#)). HP β CD treatment did not alter peripheral immune cell populations in the blood or spleens of mice after stroke.

In rats undergoing hypoxia-ischemia, a single dose of HP β CD (1 g/kg, i.p.) 30 minutes following hypoxia-ischemia reduced brain infarction size by 28.57% compared with control, and the reduction was greatest in the striatum and adjacent cortex (and the least in the hippocampus) ([Rivers et al., 2012](#)). In hippocampal slices, HP β CD treatment was neuroprotective by reducing excitotoxicity.

In a mouse model of atherosclerosis (ApoE^{-/-} mice fed Piagen's high-fat diet), two forms of cyclodextrins, cyclodextrin polymers (β CDP) vs HP β CD were administered (1 g/kg, twice a week, s.c.) for 4 weeks ([Kim et al., 2020](#)). β CDP was prepared by covalent crosslinking of cyclodextrin molecules and had a diameter of ~10 nm. β CDP treatment significantly reduced atherosclerotic lesions in the aortic arch and thoracic aorta, and reduced plaques in the aortic root, compared to treatment with monomeric HP β CD at the same dose. In an ex vivo culture study, β CDP induced superior cholesterol efflux from plaque tissue. Additionally, β CDP did not induce significant ototoxicity at a high-dose (8 g/kg), nor did it induce plasma membrane disruption (cytotoxicity, hemolytic activity), whereas HP β CD treatment reduced the outer hair cell content by 36%. Plaque stability was not affected by β CDP treatment, suggesting that β CDP exerted anti-atherogenic effects without increasing the vulnerability of the plaques. Together, cyclodextrin polymers may have greater therapeutic potential for the treatment of atherosclerosis without the systemic toxicity associated with monomeric HP β CD.



Safety: Adverse events depend on route, dose, and dosing regimen, plus there are individual differences. Ototoxicity, tinnitus, fatigue, and increased liver enzymes are frequently observed.

Types of evidence:

- 2 double-blind, randomized, uncontrolled trials in NPC1
- 4 open-label clinical trials in NPC1
- 1 case study in NPC1
- Numerous laboratory studies

Safety of VTS-270 in NPC1: In a phase I/II non-randomized, open-label, dose-escalation study in 14 NPC1 patients, monthly intrathecal treatment of VTS-270 (initial doses of 50, 200, 300, 400, or 900 mg per month) for up to 18 months resulted several treatment interruptions: 2 patients experienced grade 1 ototoxicity, 1 patient had hepatocellular carcinoma, 1 patient had caregiver hardship, and 1 patient had mastoiditis ([Ory et al., 2017](#)). No drug-related serious adverse events (SAEs) were observed. However, mid-frequency to high-frequency hearing loss was documented in all participants (14 out of 14; 100%). Greater ototoxicity was observed in patients who had not already had high-frequency hearing loss due to the NPC1 disease. One patient showed grade 3 hearing loss upon initial dosing at 400 mg, but subsequent administration of VTS-270 at a dose of 300 mg, biweekly, did not result in additional ototoxicity. The hearing loss was managed with hearing aids, which did not lead to a significant effect on daily communication. Tinnitus appeared to also be associated with VTS-270 (though not every patient could self-report it). It was limited to the post-dose period in 2 patients and persistent in 4 patients. Post-lumbar puncture headache was observed in 9 out of 14 patients (64%). Unsteadiness and fatigue were observed with doses above 600 mg, which typically occurred 24-72 hours post-dosing and was transient. The degree of impairment was classified as “clinically significant” in 3 out of 9 patients (33%) at the 600 mg dose, 6 out of 12 patients (50%) at the 900 mg dose, and 9 out of 9 participants (100%) at the 1200 mg dose.

In an open-label, long-term clinical study as part of an investigational new drug application for expanded access (IND 119856), 3 patients with NPC1 received intrathecal treatment (via lumbar puncture) of VTS-270 (dosing based on tolerability, from 200-1200 mg, every 2 weeks) for 2.5-3 years, and there were several adverse events ([Berry-Kravis et al., 2018](#)). Patient 1 experienced mild high-frequency sensorineural hearing loss, which was addressed with hearing aids such that there was no impact on conversational responses. Patient 1 also experienced persistent ataxia and tiredness at the 1200 mg dose and milder post-dose ataxia and tiredness at the 900 mg dose, lasting 3-7 days. At the 750 mg dose, these symptoms were mild and lasted under 48 hours. Patient 2 experienced mild-to-moderate

mid-to-high frequency hearing loss at doses 600 mg and above, which was addressed with hearing aids to minimize impact on function and performance at school. Patient 2 also had mild post-dose tiredness for several days after each dose of 900 and 1200 mg, but this was resolved within 24 hours and did not impact functioning after dose reduction to 750 mg. Patient 3 experienced incremental hearing loss and tinnitus with each of three 400 mg doses and has continued on a dose of 300 mg. She has moderate mid-to-high frequency hearing loss, but the use of hearing aids minimized impact to daily life and work performance. Patient 3 did not experience post-dose tiredness or gait/balance changes.

In a phase I/II, non-randomized, open-label clinical trial in 3 infants with NPC1, intravenous VTS-270 treatment (500 to 1000 mg/kg at a rate of 250 mg/kg/hour) through a peripherally inserted central catheter, twice a week for 6 weeks followed by monthly infusions for 6 months was well-tolerated and no patient experienced a drug-related adverse event ([Reynolds et al., 2021](#)). Adverse events that occurred during the study included the peripherally-inserted central catheter line erythema, elevated transaminases, fever, cough, and viral rash.

Safety of Trappsol® Cyclo™ in NPC1: In a phase I/II randomized double-blind, parallel group study with no control group, intravenous infusion of Trappsol® Cyclo™ at doses of 1500 mg/kg (n=5), 2000 mg/kg (n=4), and 2500 mg/kg (n=3) (over 8-9 hours every 2 weeks) for a 48-week period were tested in patients with NPC1 ([presentation](#) from Australian NPC Disease Foundation Annual Conference, June 25, 2021). Nine patients completed the study. The total numbers of SAEs were 9 in the 1500 mg/kg dose, 2 in the 200 mg/kg dose, and 4 in the 2500 mg/kg dose. SAEs included aspiration pneumonia and 7 hospitalizations for seizures in 2 patients in the 1500 mg/kg group; CSF leak and deterioration in hearing (Grade 2) in 1 patient in the 2000 mg/kg dose; and erythema, hand swelling, influenza B, and acute tonsillitis in 2 patients in the 2500 mg/kg dose. The total numbers of treatment-emergent adverse events (TEAEs) were 51 in the 1500 mg/kg dose, 62 in the 2000 mg/kg dose, and 72 in the 2500 mg/kg dose.

In a phase 1, randomized, double-blind, parallel group study with no control group, intravenous infusion of Trappsol® Cyclo™ at doses of 1500 mg/kg (n=6) and 2500 mg/kg (n=4) (over 8-9 hours every 2 weeks) for a 14-week period were tested in patients with NPC1 ([presentation](#) from Australian NPC Disease Foundation Annual Conference, June 25, 2021). Thirteen patients were enrolled, of whom 10 patients completed the study. One subject discontinued due to hypersensitivity and 2 patients discontinued after multiple doses, due to transient changes in hearing. There were 13 TEAEs in the 1500 mg/kg group with no SAEs. There were 27 TEAEs and 8 SAEs in the 2500 mg/kg group, 3 of which related to hearing loss,

which were all transient. CSF to plasma ratio was 2% at 8 hours post-infusion, while the ratio increased to 11-16% at 12 hours.

Safety of mixed HPβCD formulations in NPC1 patients: In an open-label long-term study, both VTS-270 and Trappsol® Cyclo™ were used in the treatment of 12 NPC1 patients, and no safety issues were observed ([Hastings et al., 2019](#)). The route of treatment varied with some people receiving intravenous doses throughout the study duration while others received intrathecal treatment followed by intravenous treatment. Intravenous treatment lasted 17-92 months, followed by an addition of intrathecal treatment for 10-74 months in some patients. For patients receiving both formulations, the vast majority of their treatments were with Trappsol® Cyclo™. Severe adverse events were attributed to devices (not the therapeutic) and included post-operative hemorrhage following placement of the Ommaya reservoir (a device implanted under the scalp for CSF delivery; 1 patient), Port-a-Cath infections (3 patients), and Ommaya infection/meningitis (1 patient). The most common adverse events were grade 1 and 2 and included: infusion reactions with nausea (intravenous and intrathecal) or headache (intrathecal) and increased seizure activity for up to 24 hours following intrathecal treatment.

In 4 patients with prior history of seizure activity, increased seizure activity occurred. Two patients experienced transient worsening of ataxia, dysarthria and worsened fine motor control following high-dose (1000 mg) intra-Ommaya infusions. One patient experienced increased lethargy and ataxia for 1 week following intrathecal administration at a dose of 600 mg but experienced no adverse events with a 500 mg dose. Patients also experienced periodic viral infections, otitis, sinusitis, diarrhea, and pneumonias not attributable to HPβCD. Two patients reported mild hearing loss in high frequencies with intrathecal treatment, but no patient experienced hearing loss as a result of intravenous therapy. Laboratory assessments (complete blood counts, chemistries, lipid panels, coagulation studies and urinalyses) did not show any trend or abnormalities.

Safety data from laboratory/animal studies: In normal cats and a feline model of NPC1, HPβCD treatment showed a dose-dependent increase in hearing threshold ([Ward et al., 2010](#)). In normal cats, HPβCD treatment caused a significant increase in hearing threshold following a single subcutaneous dose of 8000 mg/kg (Sigma Aldrich, dissolved in 0.9% sodium chloride) or a single intrathecal dose of 120 mg, and the effect persisted for at least 12 weeks. Repeated weekly subcutaneous administration of HPβCD at a dose of 4000 mg/kg resulted in a similar increase in hearing threshold. In NPC cats (produced from a line bred for autosomal recessively inherited NPC disease), weekly subcutaneously administered 4000 mg/kg or 8000 mg/kg HPβCD treatment resulted in higher hearing thresholds than any untreated cats with NPC disease. Intrathecal HPβCD treatment in NPC cats showed no auditory

responses to even the highest sound intensity of 125 dB. In 2 normal cats, Trappsol® Cyclo™ was administered subcutaneously as a single dose of 8000 mg/kg or intrathecally as a single dose of 4000 mg/kg brain weight (120 mg), and the changes in brain stem auditory evoked response was comparable to that seen with the Sigma product. Hearing threshold in 2 cats treated intrathecally increased from 69 dB and 72 dB to 87 dB and 90 dB following Trappsol® Cyclo™. Hearing threshold in 2 cats treated subcutaneously increased from 69 dB and 72 dB to 87 dB in both cats following Trappsol® Cyclo™.

In a mouse model of Alzheimer's (TgCRND8 mice), intracerebroventricular Trappsol® Cyclo™ treatment (40 mg/kg/day) for 14 days enhanced cathepsin activity to clear stored substrates in lysosomes, but also delayed autophagosome maturation and inhibited autophagosome-lysosome fusion ([Yang et al., 2017](#)). The delay in autophagosome maturation could, over long periods, be detrimental to cellular homeostasis due to the gradual build-up of autophagy substrates, which would be a concern for long-term treatment such as would be required for the treatment of Alzheimer's disease.

In a mouse model of atherosclerosis (ApoE^{-/-} mice fed Piagen's high-fat diet), a high-dose HPβCD treatment (8 g/kg, s.c.) reduced the outer hair cell content by 36% ([Kim et al., 2020](#)). Interestingly, treatment with the β-cyclodextrin polymer (βCDP) did not induce significant ototoxicity even at the same high dose.

In wild-type mice, intranasal treatment with HPβCD significantly increased lung weight which was due to inflammation and accumulation of macrophages containing dense eosinophilic material with neutrophilic and lymphocytic inflammation ([Erickson et al., 2018](#)). This pathology was enhanced in a mouse model of NPC1 (Npc1nmf164 homozygous mice).

An old toxicology review of HPβCD reported that toxicity was variable depending on the duration of the treatment and the route ([Gould et al., 2005](#)).

- Oral dosing showed the least amount of toxicity. In a 12-month study in dogs, HPβCD administration by oral gavage at doses of 500, 1000, and 2000 mg/kg/day resulted in softened feces and urinary tract histological changes at the 2000 mg/kg/day, but no changes at 500 and 1000 mg/kg/day doses.
- Intravenous dosing has resulted in histopathological changes in lungs, liver, and kidney, but these findings were reversible. In rats, a single intravenous dose of 2250 mg/kg HPβCD was not tolerated and resulted in premature deaths and adverse clinical signs, including decreased activity, breathing irregularities, and the body being cold to the touch. An intravenous dose of 1000 mg/kg did not result in premature deaths or adverse clinical signs. In rats continuously infused for 4-7 days with 225 mg/kg/day of HPβCD resulted in foamy macrophage infiltration of the lung (with some



associated alveolitis hemorrhage and atelectasis), renal cortical tubular vacuolation of the proximal convoluted tubules, and mild reduced splenic extramedullary hematopoiesis. In rats, a continuous intravenous infusion of 2400 mg/kg/day of HP β CD resulted in reduced water consumption, reduced plasma cholesterol, changes in the kidney (increased kidney weight and moderate renal cortical tubular vacuolation), and mild foamy alveolar macrophages in the lung.

- Three-month intravenous dosing studies were conducted in rats and dogs, testing HP β CD doses of 50, 100 or 400 mg/kg/day. In the rat, there were no adverse findings at 50 mg/kg/day, but at 100 mg/kg/day, there were minimal histological changes in the urinary bladder (swollen epithelial cells), swollen and granular kidney tubular cells and an increase in Kupffer cells in the liver. At 400 mg/kg/day, rats showed decreased body weight and food consumption, increased water consumption, decreased hematocrit, hemoglobin and erythrocytes, and increased creatinine, bilirubin and aspartate and alanine aminotransferase levels (AST and ALT, respectively). After a one-month recovery period, some toxicological changes had reversed, but small elevations in AST and ALT levels remained and only a partial reversal was seen for the urinary tract bladder and lung changes. In dogs, there were no adverse effects at 50 or 100 mg/kg/day, but at the 400 mg/kg/day dose, ALT, AST, and total bilirubin levels were increased. There were foamy cells in the lung and swollen epithelial cells in the urinary bladder and renal pelvis. After the recovery period, there was an incomplete recovery of the swollen renal pelvis epithelium.
- Subcutaneous dosing has caused a decrease in body weight gain, a decrease in liver weight, and nephrotoxicity, with an increase in kidney weight, proximal tubular nephrosis, and cellular vacuolation.
- Genetic toxicity studies (Ames assay, in vivo micronucleus test) have reported no evidence that HP β CD is genotoxic.
- Carcinogenicity studies showed an increase in tumors in rats that were rat-specific (e.g., pancreas and intestines). In studies in mice, HP β CD treatment in the diet (500, 2000, and 5000 mg/kg/day) for 18 months showed no effects on survival or total tumor incidence.
- No effects have been seen in embryo-fetal development in rats or rabbits. In an intravenous embryo-fetal development study in rats, HP β CD treatment at a dose of 400 mg/kg/day caused slight maternal toxicity, but there were no adverse effects observed in the offspring. In a study in rabbits, there were no adverse effects to the offspring at doses of up to 400 mg/kg/day. In an oral teratogenic and embryotoxicity study in rats, maternal toxicity, embryotoxicity and teratogenicity were not observed at doses of up to 400 mg/kg/day. In an oral teratogenic and embryotoxicity study in rabbits, slight maternal toxicity and embryotoxicity was present at 1000 mg/kg.

Drug interactions: Drug interactions have not been well-studied or documented.

Sources and dosing: VTS-270 (Adrabetadex) is under clinical development by Mandos LLC. VTS-270 received Breakthrough Therapy designation status by the FDA for the treatment of NPC1 and is currently undergoing a phase 2b/3 clinical trial ([PRNewswire.com](https://www.prnewswire.com)). In a phase 2b/3 trial in NPC1, VTS-270 will be administered every 2 weeks via lumbar intrathecal infusion at a dose of 900-1800 mg ([NCT02534844](https://clinicaltrials.gov/ct2/show/study/NCT02534844)).

Trappsol® Cyclo™ is under development for the treatment of both NPC1 and Alzheimer's disease ([CycloTherapeutics.com](https://www.cyclotherapeutics.com)). In a phase 3 trial in NPC1, Trappsol® Cyclo™ will be administered intravenously at a 2000 mg/kg dose ([CycloTherapeutics.com](https://www.cyclotherapeutics.com)).

Research underway: There are currently 4 ongoing clinical studies testing HPβCD ([ClinicalTrials.gov](https://clinicaltrials.gov)). These are all testing HPβCD in Niemann-Pick Disease, and all are “active, but no longer recruiting patients”, as of January 2022. In a phase 2b/3 randomized, double-blind, sham-controlled trial in NPC1, VTS-270 will be administered every 2 weeks via lumbar intrathecal infusion at a dose of 900-1800 mg ([NCT02534844](https://clinicaltrials.gov/ct2/show/study/NCT02534844)). Primary outcome measures include NPC severity scale (NPC-SS) and the Clinical Global Impression of Change at week 52. In a double-blind randomized, placebo-controlled phase 3 trial in NPC1, 93 patients will be recruited at 23 sites across 9 countries, and Trappsol® Cyclo™ will be administered intravenously at a 2000 mg/kg dose ([CycloTherapeutics.com](https://www.cyclotherapeutics.com)). The duration of the trial is 96 weeks, and its primary endpoint is the NPC Composite Severity Score. Trappsol® Cyclo™ is also under development for Alzheimer's disease, with IND clearance to advance to a phase 2 study.

There are studies suggesting that HPβCD may be safer as a treatment when it is administered in a polymer form rather than a monomer. In a mouse model of atherosclerosis (ApoE^{-/-} mice fed Piagen's high-fat diet), two forms of cyclodextrins, cyclodextrin polymers (βCDP) vs HPβCD were compared and the βCDP was efficacious in reducing atherosclerotic lesions without inducing ototoxicity or disrupting plasma membranes (cytotoxicity, hemolytic activity)([Kim et al., 2020](#)). Thus, cyclodextrin polymers may have greater therapeutic potential without the systemic toxicity associated with monomeric HPβCD. Further studies are needed.

Search terms:

Pubmed, Google: Hydroxypropyl-β-cyclodextrin, Abrabetadex, VTS-270, Trappsol Cyclo

- + meta-analysis
- + cognitive
- + brain
- + clinical trial
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- + neuropathic pain

Websites visited for Hydroxypropyl- β -cyclodextrin, Abrabetadex, VTS-270, Trappsol Cyclo :

- [Clinicaltrials.gov](https://clinicaltrials.gov)
- [NIH RePORTER](https://reporter.nih.gov)
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com (0)
- WebMD.com (0)
- [PubChem](https://pubchem.ncbi.nlm.nih.gov)
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