JOURNÉE NATIONALE
PATIENTS & FAMILLES
Niemann-Pick C

Traitements spécifiques de la maladie de Niemann Pick C

20 NOV 2026

Dr Anne-Sophie Guémann

Liens d’intérêts

- Invitation aux congrès:

Sanofi, Takeda, PTC, Chiesi

- Études thérapeutiques:

Denali, PTC, Biomarin

- Rédaction et réalisation de supports éducatifs :

Chiesi, Sanofi, Takeda, Biomarin

Une histoire récente…

- **Années 1920 :** Albert Niemann et Ludwig Pick décrivent un groupe de maladies hétérogènes caractérisées par une **hépatosplénomégalie** (augmentation du volume du foie et de la rate) et une **accumulation anormale de lipides** dans les tissus, parfois associées à une atteinte neurologique.

- **1958 :** Crocker et Farber proposent une première classification distinguant les **types A, B et C** de la maladie de Niemann-Pick, sur la base de leurs caractéristiques cliniques.

- **À partir des années 1960 :** Les avancées biochimiques permettent de distinguer deux mécanismes physiopathologiques :
  - **Types A et B :** déficit enzymatique en sphingomyélinase acide, responsable d'une accumulation de sphingomyéline.
  - **Type C :** anomalie du trafic intracellulaire du cholestérol, entraînant son accumulation dans les compartiments endolysosomaux (années 1980)



Albert Niemann Ludwig Pick

Sidney Farber



Le Docteur Sidney Farber, en 1966



Dr. Allen Crocker, 85;

Ce qu’il se passe à l’intérieur de la cellule:

NIH Public Access
Author Manuscript
Expert Rev Mol Med. Author manuscript; available in PMC 2009 March 30.

Published in final edited form as:
Expert Rev Mol Med. ; 10: e26. doi:10.1017/S146239940800080X.

The pathogenesis of Niemann-Pick type C disease: a role for autophagy?

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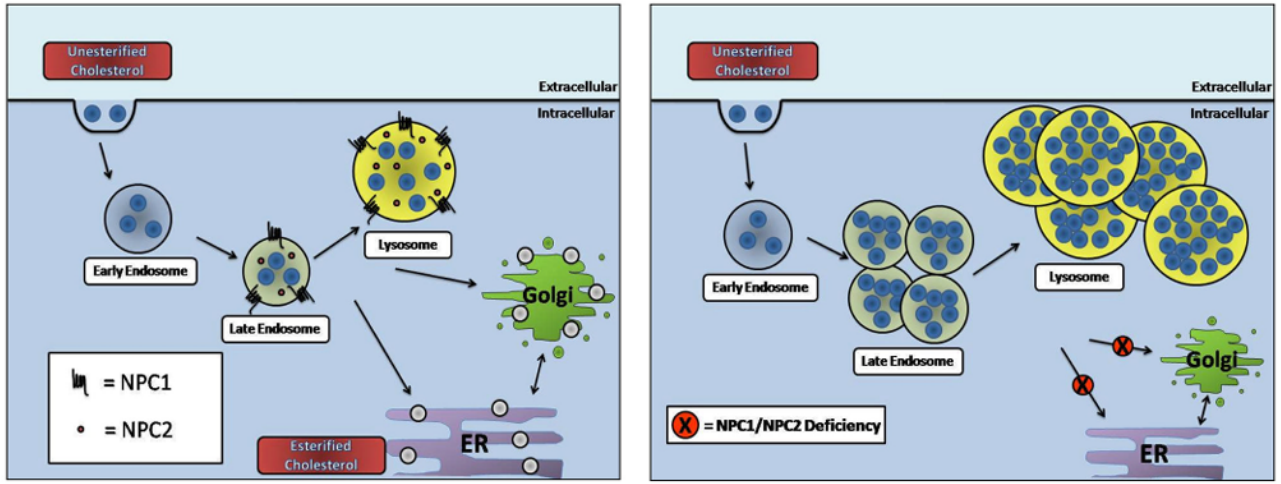
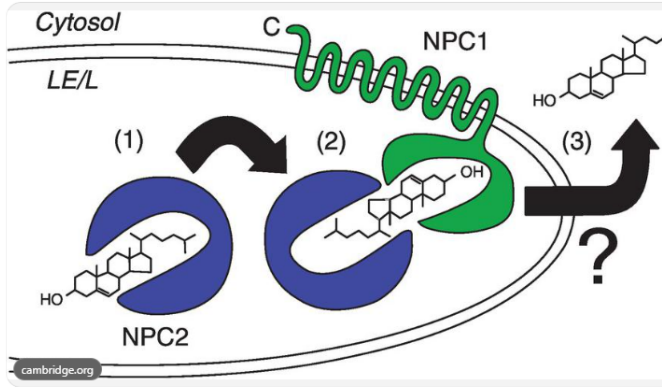


Figure 1. Lipid trafficking defects in Niemann-Pick type C disease

Left panel. Under normal conditions, lipoprotein cholesterol particles enter the endosomal network after binding to cell surface receptors. Unesterified cholesterol and companion lipids are trafficked from the endosomal/lysosomal system to the Golgi, endoplasmic reticulum and other intracellular compartments.

Right panel. NPC1 or NPC2 loss of function inhibits the egress of unesterified cholesterol and sphingolipids from late endosomes and lysosomes, resulting in their accumulation at these sites and a paucity of these lipids at the intracellular compartments to which they were destined.

Abbreviation: ER, endoplasmic reticulum.



NPC1

- Située dans la membrane du lysosome.
- Permet au cholestérol de sortir du lysosome.

95 %

des patients présentent une anomalie du gène NPC1.

NPC2

- Située à l'intérieur du lysosome.
- Transporte le cholestérol jusqu'à NPC1.

5 %

des patients présentent une anomalie du gène NPC2.

- **Le lysosome** : un entrepôt de recyclage.
- **Le cholestérol** : la marchandise à redistribuer.
- **NPC2** : le livreur qui récupère la marchandise dans l'entrepôt.
- **NPC1** : la porte de sortie de l'entrepôt.
- Si le livreur ne travaille plus ou si la porte de sortie est bloquée, le résultat est le même : la marchandise s'accumule dans l'entrepôt.
- Et paradoxalement, alors que l'entrepôt déborde de cholestérol, le reste de la cellule peut manquer de cholestérol disponible.

Traitements médicamenteux historiques

- **Années 1990 : les premières tentatives thérapeutiques**



- **Objectif : réduire l'accumulation de cholestérol**
- Utilisation de traitements hypocholestérolémiants: **lovastatine, cholestyramine, acide nicotinique**, associés à des mesures diététiques.
- Étude de Patterson et al. (1993) chez 25 patients.



- **Diminution du cholestérol hépatique et sanguin**



- Mais aucun bénéfice démontré concernant l'évolution neurologique
- Abandon progressif de cette stratégie au profit de traitements ciblant davantage les mécanismes intracellulaires de la maladie.



Miglustat : des mécanismes d'action multiples

Review

Miglustat in Neuronopathic Lysosomal Storage Disorders: Biological Rationale, Clinical Evidence, and Limits of Repurposing

Patryk Lipiński [1] and Grzegorz Węgrzyn [2,*]

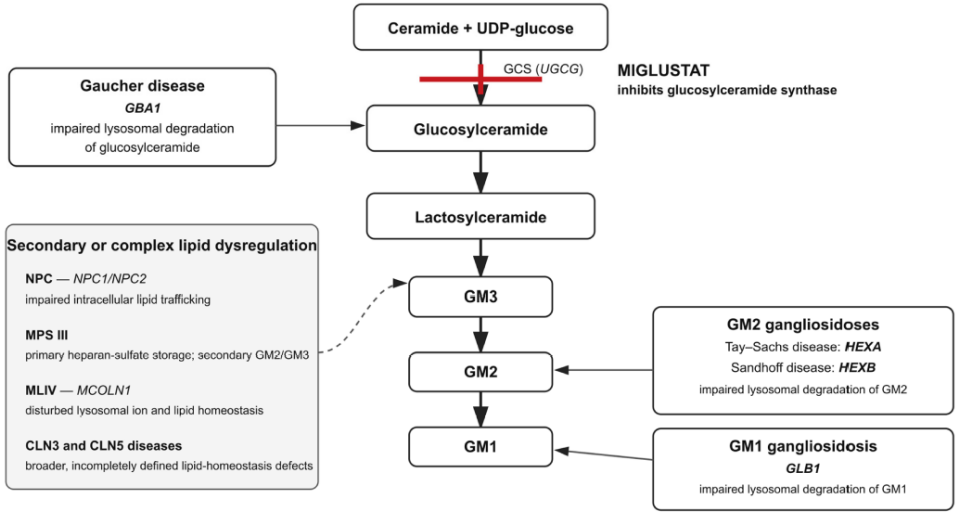


Figure 2. Glycosphingolipid pathway and the stage of action of miglustat. Miglustat inhibits UDP-glucose:ceramide glucosyltransferase, commonly termed glucosylceramide synthase (GCS), thereby reducing the formation of glucosylceramide and downstream glycosphingolipids (the inhibition of the reaction (makred by red arrow) by miglustat is indicated by a horizontal red line). In Gaucher disease and GM1 and GM2 gangliosidoses, the primary molecular defect directly affects glycosphingolipid degradation. In Niemann–Pick disease type C, mucopolysaccharidosis type III, mucolipidosis type IV, and CLN3 and CLN5 diseases, glycosphingolipid abnormalities are secondary or form part of broader disturbances of lysosomal lipid homeostasis. Biochemical proximity to GCS does not by itself predict neurological response to miglustat. Abbreviations: GBA1, β-glucocerebrosidase; GCS, glucosylceramide synthase; GLB1, β-galactosidase; HEXA, β-hexosaminidase subunit α; HEXB, β-hexosaminidase subunit β; MLIV, mucolipidosis type IV; MPS III, mucopolysaccharidosis type III; NPC, Niemann–Pick disease type C; UDP, uridine diphosphate.

1. Réduction de la synthèse des glycosphingolipides

- Inhibition de la glucosylcéramide synthase (GCS).
- Diminution de la production et de l'accumulation de certains glycosphingolipides dans les cellules.

RESEARCH ARTICLE

Reducing GBA2 Activity Ameliorates Neuropathology in Niemann-Pick Type C Mice

André R. A. Marques[1*], Jan Aten[2*], Roelof Ottenhoff[1], Cindy P. A. A. van Roomen[1], Daniela Herrera Moro[1], Nike Claessen[2], Maria Fernanda Vinueza Veloz[2], Kuikui Zhou[3], Zhanmin Lin[3], Mina Mirzaian[1], Rolf G. Boot[1], Chris I. De Zeeuw[2,4], Herman S. Overkleeft[3], Yildiz Yildiz[3], Johannes M. F. G. Aerts[1]*

2. Inhibition de la β-glucosidase 2 (GBA2)

- Enzyme impliquée dans le métabolisme du glucosylcéramide en dehors des lysosomes.
- Son inhibition pourrait améliorer l'acidification lysosomale et le trafic intracellulaire des lipides.

3. Régulation de l'homéostasie calcique

- L'accumulation de sphingosine perturbe les réserves de calcium lysosomal.
- Le miglustat pourrait contribuer à restaurer l'équilibre calcique et améliorer le fonctionnement cellulaire.

Review

Neurodegeneration in Niemann–Pick Type C Disease: An Updated Review on Pharmacological and Non-Pharmacological Approaches to Counteract Brain and Cognitive Impairment

Ida Cariati [1,2], Laura Masuelli [3], Roberto Bei [2], Virginia Tancredi [4,5], Claudio Frank [6] and Giovanna D'Arcangelo [4,5,*]

4. Effets neuroprotecteurs

- Diminution de l'accumulation lipidique et ralentissement de la neurodégénérescence dans les modèles animaux.
- Amélioration de la survie des neurones de Purkinje.
- Restauration partielle de la plasticité synaptique, impliquée dans l'apprentissage et la mémoire.

Miglustat : premiers résultats précliniques (2001)

- **Objectif :** Évaluer si la réduction de la synthèse des glycosphingolipides permet de ralentir la neurodégénérescence dans la NPC.

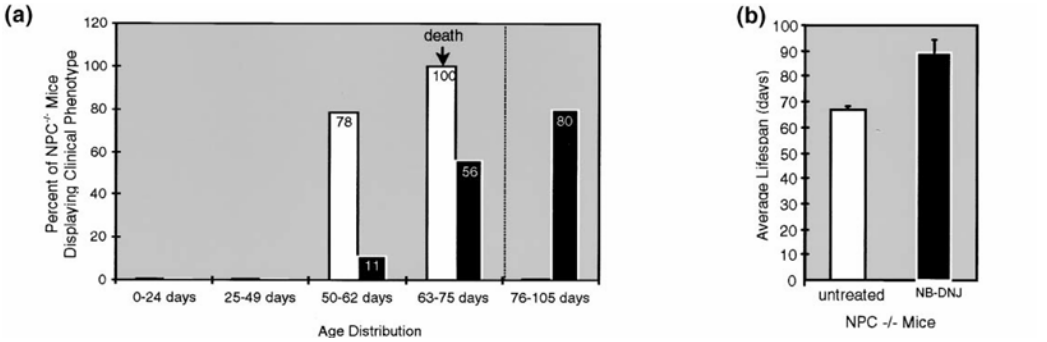
- **Méthodologie :**
- Modèles animaux de NPC : souris et chats.
- Administration de NB-DNJ (miglustat), inhibiteur de la glucosylcéramide synthase.

- **Résultats :**
- **Retard d'apparition des troubles neurologiques** (ataxie, tremblements).
- Entre 50 et 62 jours : troubles neurologiques chez **78 % des souris non traitées contre 11 % des souris traitées**.
- **Prolongation de la survie moyenne d'environ 30 %** chez les souris traitées.
- Diminution de l'accumulation cérébrale des gangliosides GM2 et GM3.
- Réduction des lésions neuronales, avec une meilleure préservation des cellules de Purkinje.

Critical role for glycosphingolipids in Niemann-Pick disease type C

Mark Zervas*‡, Kyra L. Somers†, Mary Anna Thrall†, and Steven U. Walkley*

Figure 1



*N*B-DNJ treatment in NPC mice and cats was found to delay the onset of clinical neurological disease, to increase longevity (murine NPC), and to reduce cellular pathology in the cerebellum. **(a)** The majority of untreated NPC mice showed a well-defined clinical phenotype (ataxia and intention tremor) between 50 and 62 days of age; by 63–75 days of age, clinical neurological disease and lethality were observed in all untreated NPC mice (open bars). In contrast, far fewer *N*B-DNJ-treated mice showed the clinical phenotype, and all were viable within this time frame (solid bars). NPC mice treated with *N*B-DNJ lived to 76–105 days of age, with many of them developing the clinical phenotype during this period. **(b)** An evaluation of longevity in *N*B-DNJ-treated versus untreated NPC mice showed that treated animals lived to 89 ± 5 days (average ± SEM) (solid bar) versus untreated mice, which lived to 67 ± 1 day (open bar). **(c)** Time

Miglustat : premier essai clinique randomisé

- **Patterson et al. — Lancet Neurology, 2007**

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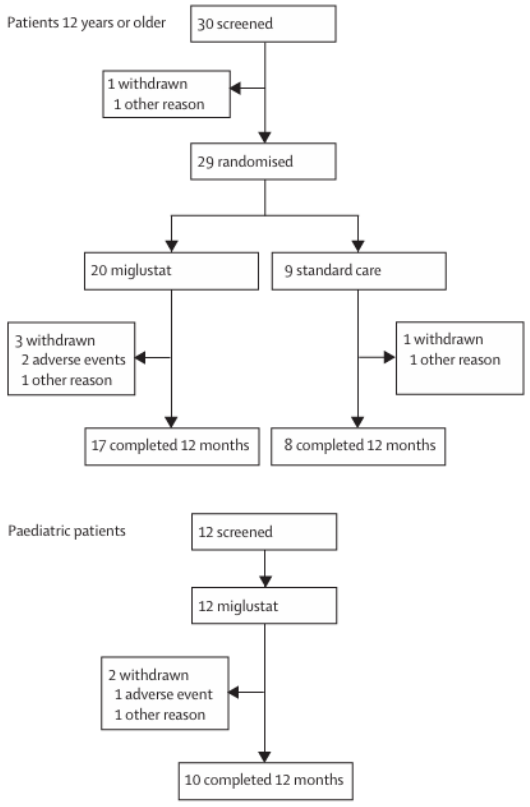
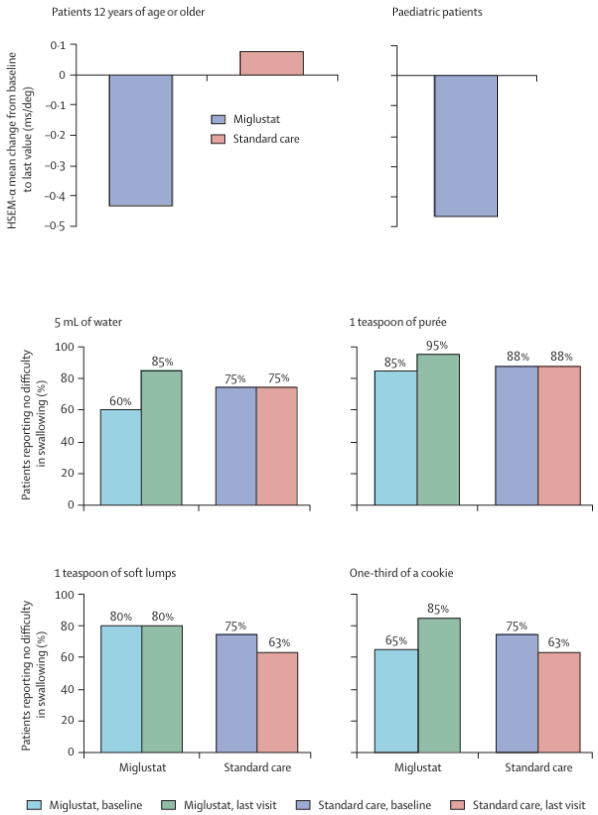
FAST TRACK — ARTICLES · Volume 6, Issue 9, P765-772, September 2007 · Download Full Issue

Miglustat for treatment of Niemann-Pick C disease: a randomised controlled study

Marc C Patterson, FRACP [a] · Darleen Vecchio [a] · Helena Prady [b] · Larry Abel, PhD [c] · James E Wraith, FRCPCH [b]

- **Objectif :** Évaluer l'efficacité du miglustat sur la progression des manifestations neurologiques de la maladie de Niemann-Pick C.
- **Méthodologie :**
- Etude prospective, randomisée, contrôlée, ouverte, sur 12 mois.
- 29 patients ≥ 12 ans : 20 sous miglustat (200 mg × 3/j) versus 9 avec soins standards.
- 12 enfants de 4 à 11 ans supplémentaires, tous traités par miglustat.
- Critère principal : vitesse des saccades oculaires horizontales.





- **Résultats :**
- Évolution favorable de la vitesse des saccades oculaires horizontales, avec une différence significative après exclusion des patients sous benzodiazépines (p = 0,028)..
- Stabilisation ou amélioration de certains paramètres neurologiques : déglutition, marche et audition.

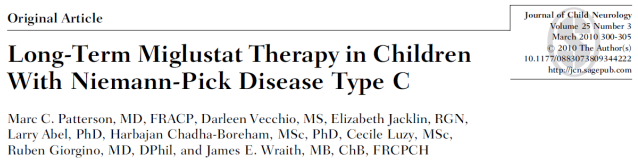
- **Déglutition:** amélioration, notamment pour les aliments solides (p = 0,044).

- **Marche :** tendance à un ralentissement de la dégradation (p = 0,052).

- **Audition :** stabilisation observée sous traitement.

- **Tolérance :** effets indésirables principalement digestifs (diarrhées, flatulences) et perte de poids.

Miglustat : suivis à 24 mois (2010)



Original Article

Long-Term Miglustat Therapy in Children With Niemann-Pick Disease Type C

Marc C. Patterson, MD, FRACP, Darleen Vecchio, MS, Elizabeth Jacklin, RGN, Larry Abel, PhD, Harbajan Chadha-Boreham, MSc, PhD, Cecile Luzy, MSc, Ruben Giorgino, MD, DPhil, and James E. Wraith, MB, ChB, FRCPCH

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http://jcn.sagepub.com



Miglustat in adult and juvenile patients with Niemann–Pick disease type C: Long-term data from a clinical trial

James E. Wraith [a,*], Darleen Vecchio [b], Elizabeth Jacklin [a], Larry Abel [c], Harbajan Chadha-Boreham [d], Cécile Luzy [d], Ruben Giorgino [d], Marc C. Patterson [e]

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[b] Columbia University Medical Center, Departments of Neurology and Pediatrics, NY, USA
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[d] Actelion Pharmaceuticals Ltd., Allschwil, Switzerland
[e] Department of Neurology, Mayo Clinic, Rochester, MN, USA

- **Patterson et al., 2010 — Journal of Child Neurology**
- **Objectif :** Évaluer l'évolution neurologique après 24 mois de traitement par miglustat.
- **Méthodologie :**
- Étude prospective, ouverte, non contrôlée. Pas de groupe contrôle
- 12 enfants de 4 à 11 ans inclaubles (avec tous au moins une atteinte neuro/ophtalmo)
- 10 enfants évalués après 24 mois de traitement.
- Évaluation des mouvements oculaires, de la marche et de la déglutition.
- **Résultats à 24 mois :**
- **80 % des enfants (8/10)** considérés comme neurologiquement stables selon les critères de l'étude.
- **Marche :** stabilité chez 8/10 enfants (80 %).
- **Déglutition :** préservée chez 9/10 enfants (90 %), déjà normale à l'inclusion.
- **Mouvements oculaires :** stables ou améliorés chez 6/9 enfants évaluables (67 %).
- **Tolérance :** principalement diarrhées (67 %), tremblements (58 %) et perte de poids (25 %).
- **Conclusion :** pourrait contribuer à stabiliser l'évolution neurologique chez certains enfants atteints de NPC, sans permettre de récupérer les fonctions déjà perdues

- **Wraith et al., 2010 — Molecular Genetics and Metabolism**
- **Objectif :** Évaluer la stabilisation des manifestations neurologiques après 24 mois de traitement par miglustat
- **Méthodologie :**
- Suivi prolongé des adolescents et adultes de l'essai initial.
- Deux études prospectives, ouvertes, non contrôlées, prolongeant l'essai initial de 2007.
- **Enfants (4–11 ans) :** 12 inclus, 10 évalués à 24 mois.
- **Adolescents et adultes (12–42 ans) :** 29 inclus initialement, 15 ayant terminé 24 mois de traitement.
- **Résultats :**
- Stabilisation de plusieurs fonctions neurologiques, notamment la marche et la déglutition, chez une proportion importante des patients (80% des patients pédiatriques, 68% des ados/adultes)
- **Limites :**
- Petits effectifs.
- Études d'extension sans groupe contrôle à long terme.
- Réponses variables selon les patients et la sévérité de la maladie.
- **Conclusion :** Le miglustat peut ralentir la progression neurologique, mais ne permet pas de corriger les lésions déjà constituées.

Suivi des adultes à long terme (2018)

Nadjar *et al. Orphanet Journal of Rare Diseases* (2018) 13:175
https://doi.org/10.1186/s13023-018-0913-4

Orphanet Journal c
Rare Disease

RESEARCH Open Access

Adult Niemann-Pick disease type C in France: clinical phenotypes and long-term miglustat treatment effect

Yann Nadjar[1*], Ana Lucia Hütter-Moncada[2], Philippe Latour[3], Xavier Ayrignac[4], Elsa Kaphan[5], Christine Tranchant[6,21,22], Pascal Cintas[7], Adrian Degardin[8], Cyril Goizet[9], Chloe Laurencin[10], Lionel Martzolff[11], Caroline Tilikete[12], Mathieu Anheim[6,21,22], Bertrand Audoin[13,23], Vincent Deramecourt[14], Thierry Dubard De Gaillarbois[15], Emmanuel Roze[1,16], Foudil Lamari[17], Marie T. Vanier[18,19] and Bénédicte Héron[20]

- **47 patients** présentant une forme neurologique adolescente/adulte de NPC.
- **37 patients traités par miglustat**, avec un suivi thérapeutique pouvant atteindre 9,8 ans.
- Une association entre durée de traitement et ralentissement de l'aggravation neurologique ($p < 0,001$).
- Une meilleure survie observée chez les patients traités plus de 2 ans ($p = 0,029$).
- Une meilleure réponse lorsque le traitement est commencé à un stade neurologique moins avancé

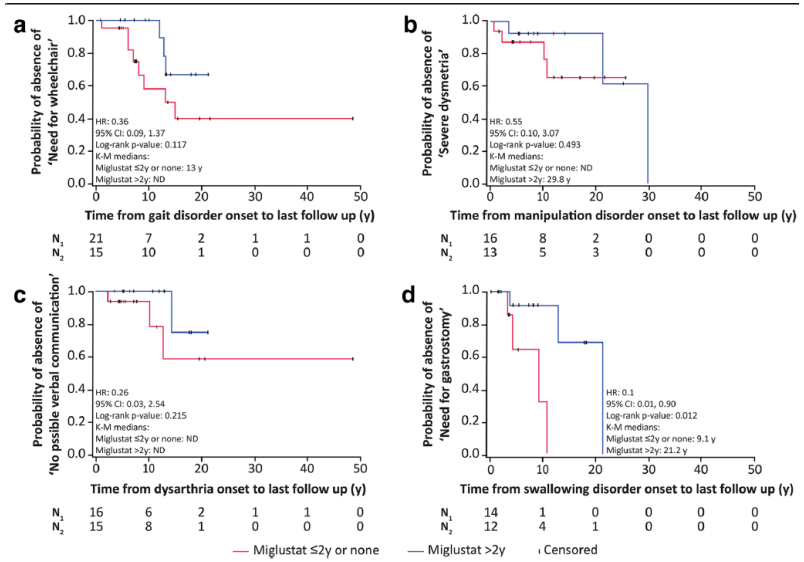

Fig. 6 Time-to-severe-event analysis for: a) impaired gait (need for wheelchair), b) manipulation (severe dysmetria); c) speech (non-verbal communication); and d) swallowing (need for gastrostomy) subscores in patients treated with miglustat for > 2 years versus untreated patients and those receiving miglustat for < 2 years. N_1, number of patients untreated or receiving miglustat for ≤2 years; N_2, number of patients treated

Conclusions

The detection of NP-C among adults in France greatly improved over the last decade, particularly since 2009 due primarily to increased awareness. A small percentage of patients who had presented in the juvenile period with non-specific, very mild neurological symptoms have shown a slow further course of disease different from that of the classical juvenile neurological form, advocating a wider concept of the adolescent/adult-onset form. Our analyses of long term follow up of miglustat therapy indicated that this pharmacological agent has had a positive impact on disease course in many patients, globally slowing down neurological deterioration and prolonging survival, although not in patients who initiated treatment at a late stage of neurological disability.

Arimoclomol

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DOI: 10.1002/jimd.12428

ORIGINAL ARTICLE

JIMD SSIEM WILEY

Efficacy and safety of arimoclomol in Niemann-Pick disease type C: Results from a double-blind, randomised, placebo-controlled, multinational phase 2/3 trial of a novel treatment

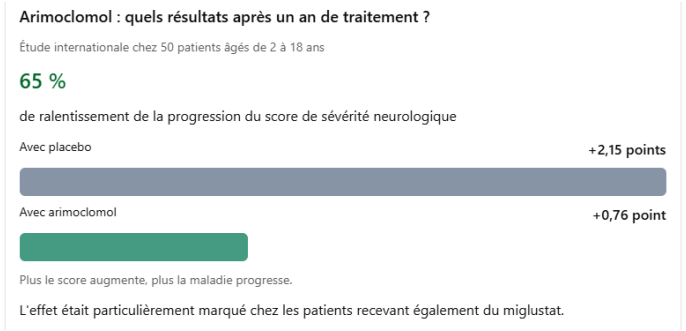
Eugen Mengel[1] | Marc C. Patterson[2] | Rosalia M. Da Riol[3] | Mireia Del Toro[4] | Federica Deodato[5] | Matthias Gautschi[6] | Stephanie Grunewald[7] | Sabine Grønborg[8] | Paul Harmatz[9] | Bénédicte Héron[10] | Esther M. Maier[11] | Agathe Roubertie[12] | Saikat Santra[13] | Anna Tylki-Szymanska[14] | Simon Day[15] | Anne Katrine Andreasen[16] | Marie Aavang Geist[16] | Nikolaj Havnsøe Torp Petersen[16] | Linda Ingemann[16] | Thomas Hansen[16] | Thomas Blaettler[16] | Thomas Kirkegaard[16] | Christine í Dali[16]

- **Objectif :** Évaluer l'efficacité et la tolérance de l'arimoclomol pour ralentir la progression neurologique de la maladie de Niemann-Pick C.
- **Arimoclomol:** petite molécule qui passe la barrière hémato encéphalique et peut ainsi passer dans le cerveau.
- Cette molécule permettrait d'amplifier la réponse naturelle au stress cellulaire et de favoriser la fonction lysosomale.
- Préserverait la fonction cellulaire et préviendrait de la mort cellulaire les cellules qui sont soumises à un stress lysosomal
- **Méthodologie :**
- Étude internationale, randomisée, en double aveugle, contre placebo.
- Réalisée de 2016 à 2018 (publiée en 2021)
- 50 patients inclus, âgés de 2 à 18 ans.
- 34 patients sous arimoclomol et 16 sous placebo, pendant 12 mois.
- 78 % des patients recevaient également du miglustat.

Efficacy and safety of arimoclomol in Niemann-Pick disease type C: Results from a double-blind,randomised, placebo-controlled,multinational phase2/3 trial of a novel treatment

Référence : Mengel E. et al. J Inherit Metab Dis. 2021;44:1463–1480. DOI : 10.1002/jimd.12428.

- **Résultats principaux :**
- **Réduction de 65 % de la progression neurologique annuelle** sous arimoclomol par rapport au placebo (p = 0,046).
- Progression du score NPCCSS à 5 domaines : +0,76 point sous arimoclomol contre +2,15 points sous placebo.
- **Stabilisation neurologique observée dans le sous-groupe recevant également du miglustat** (p = 0,006).
- Tolérance globalement favorable, avec toutefois des effets indésirables nécessitant une surveillance : effets indésirables principalement digestifs (vomissements), infections respiratoires, perte de poids et élévation de la créatininémie. Trois arrêts de traitement pour effets indésirables, notamment réactions allergiques (urticaire, angio-œdème).



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ORIGINAL ARTICLE

JIMD SSIEM WILEY

Efficacy and safety of arimoclomol in Niemann-Pick disease type C: Results from a double-blind, randomised, placebo-controlled, multinational phase 2/3 trial of a novel treatment

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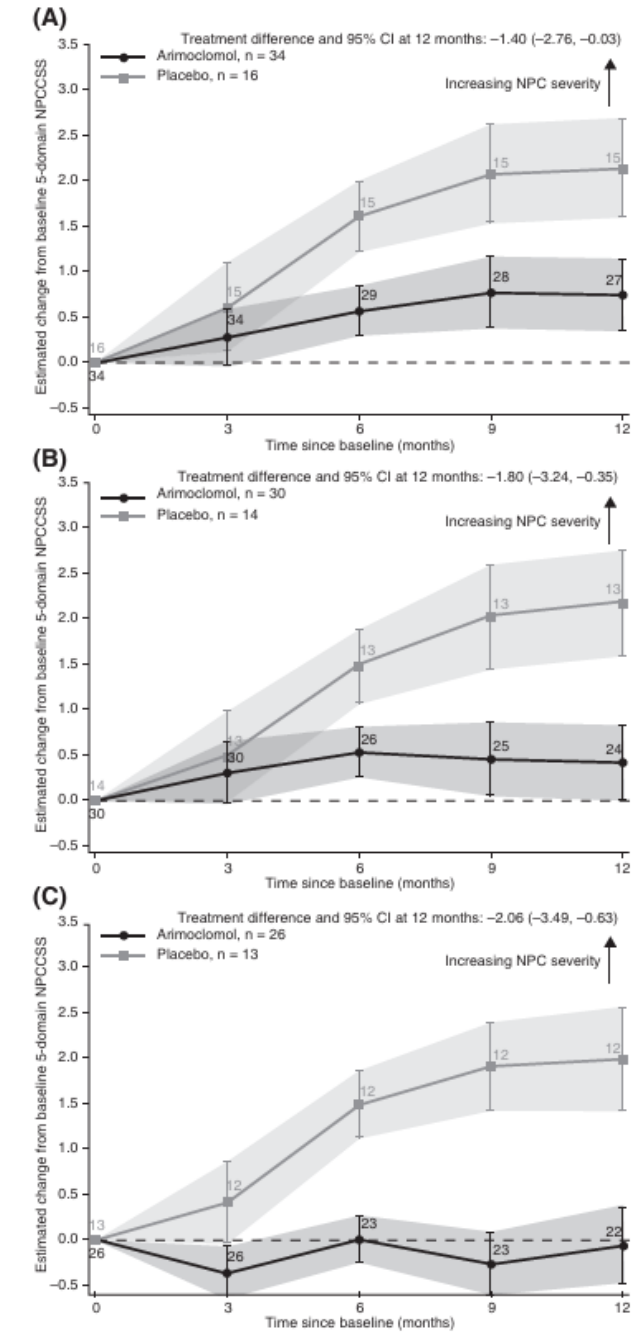


FIGURE 2 5-domain NPCCSS score observed change from baseline at month 12: A, Overall (N = 50; full analysis set); B, in patients aged ≥4 years (n = 44); C, in patients receiving miglustat (n = 39). The solid line represents least-squares mean estimates ± SE based on data obtained while patients were exposed to study treatment. The mixed model for repeated measures included the main effect of baseline and stratum, respectively, and interaction between treatment and visit. Change from baseline and absolute estimates correspond to the at-baseline overall average patient. Numbers of patient are presented for each time point. CI, confidence interval; NPC, Niemann-Pick disease type C; NPCCSS, Niemann-Pick disease type C Clinical Severity Scale

PNDS (2021)

1. Miglustat — Traitement de référence

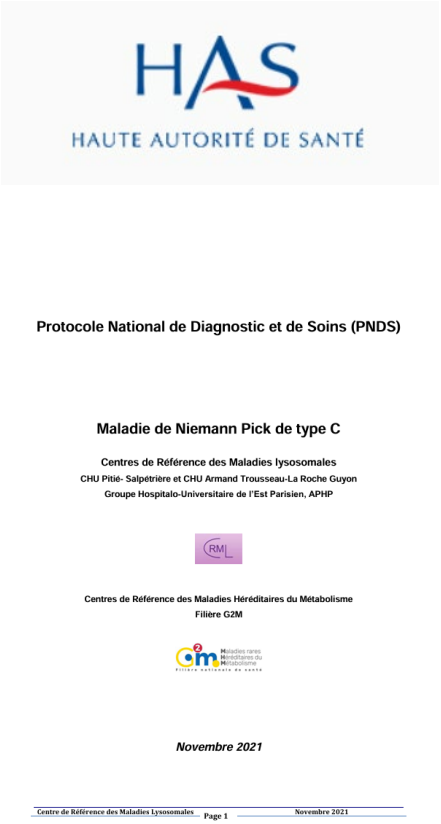
- AMM en France depuis 2009 pour les manifestations neurologiques de la NPC.
- Inhibiteur de la synthèse des glycosphingolipides, capable de traverser la barrière hémato-encéphalique.
- **Objectif : stabiliser ou ralentir la progression neurologique.**
- À débuter précocement dès l'apparition des signes neurologiques, y compris oculomoteurs.
- Aucun bénéfice démontré sur les atteintes viscérales isolées.
- Principaux effets indésirables : diarrhées, douleurs abdominales, perte de poids.

2. Arimoclomol — Traitement en accès dérogatoire

- Disponible en ATU / accès précoce depuis février 2021.
- Renforcement de la réponse au stress cellulaire, notamment via HSP70.
- Ralentissement de la progression neurologique observé dans un essai clinique, particulièrement chez les patients recevant également du miglustat.

3. Autres approches thérapeutiques étudiées

- **N-acétyl-L-leucine :** action potentielle sur les cellules de Purkinje.
- **Hydroxypropyl-β-cyclodextrine :** réduction de la surcharge lipidique neuronale.
- **Nouveaux inhibiteurs de substrat :** recherche d'une meilleure tolérance.
- **Greffes et thérapie génique :** absence de bénéfice neurologique établi chez l'humain.
- **À retenir :** Les traitements visent principalement à ralentir la progression neurologique. La prise en charge reste multidisciplinaire et symptomatique.


HAS
HAUTE AUTORITÉ DE SANTÉ

Protocole National de Diagnostic et de Soins (PNDS)

Maladie de Niemann Pick de type C

Centres de Référence des Maladies lysosomales
CHU Pitié- Salpétrière et CHU Armand Trousseau-La Roche Guyon
Groupe Hospitalo-Universitaire de l'Est Parisien, APHP

Centres de Référence des Maladies Héréditaires du Métabolisme
Filière G2M

Novembre 2021

Centre de Référence des Maladies Lysosomales Page 1 Novembre 2021

PNDS (2021)

1. Miglustat — Traitement de référence

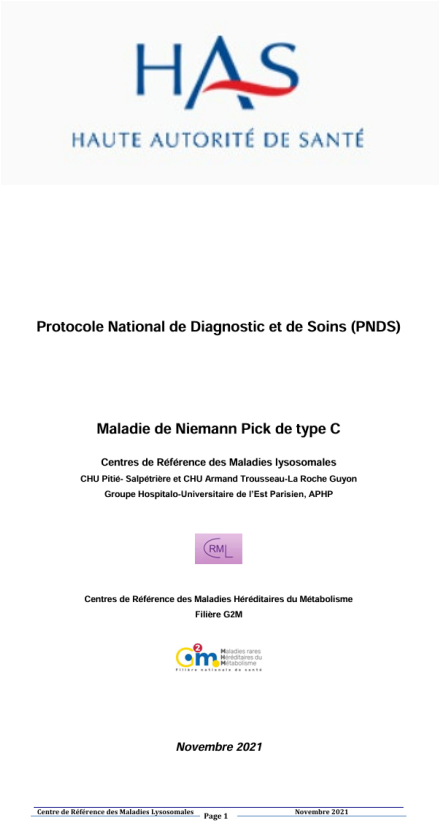
- AMM en France depuis 2009 pour les manifestations neurologiques de la NPC.
- Inhibiteur de la synthèse des glycosphingolipides, capable de traverser la barrière hémato-encéphalique.
- **Objectif : stabiliser ou ralentir la progression neurologique.**
- À débuter précocement dès l'apparition des signes neurologiques, y compris oculomoteurs.
- Aucun bénéfice démontré sur les atteintes viscérales isolées.
- Principaux effets indésirables : diarrhées, douleurs abdominales, perte de poids.

2. Arimoclomol — Traitement en accès dérogatoire

- Disponible en ATU / accès précoce depuis février 2021.
- Renforcement de la réponse au stress cellulaire, notamment via HSP70.
- Ralentissement de la progression neurologique observé dans un essai clinique, particulièrement chez les patients recevant également du miglustat.

3. Autres approches thérapeutiques étudiées

- **N-acétyl-L-leucine :** action potentielle sur les cellules de Purkinje.
- **Hydroxypropyl-β-cyclodextrine :** réduction de la surcharge lipidique neuronale.
- **Nouveaux inhibiteurs de substrat :** recherche d'une meilleure tolérance.
- **Greffes et thérapie génique :** absence de bénéfice neurologique établi chez l'humain.
- **À retenir :** Les traitements visent principalement à ralentir la progression neurologique. La prise en charge reste multidisciplinaire et symptomatique.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Filière G2M

Novembre 2021

Centre de Référence des Maladies Lysosomales Page 1 Novembre 2021

Régime et miglustat

MIGLUSTAT

↓

Inhibition des dissacharidases intestinales

↓

Accumulation des sucres non digérés et fermentation intestinale

↓

Troubles digestifs : diarrhées, douleurs, ballonnements, gaz

Les principaux disaccharides sont :

- Le LACTOSE formé de galactose + glucose
- Le SACCHAROSE formé de fructose + glucose
- Le MALTOSE formé de glucose + glucose

GROUPE D'ALIMENTS	AUTORISES car NE CONTENANT PAS ou TRES PEU DE DISACCHARIDES	DECONSEILLES car contenant des DISACCHARIDES 1ére étape	*Pourquoi*
VIANDES POISSON OEUF	• Toutes les **viandes**, volailles fraîches ou surgelés, nature • **Charcuterie** SANS lactose • Tous les **poissons** frais ou surgelés, nature, conserve à l'huile • **Coquillages, crustacés** • **Œufs** poule, caille, oie…	• Toutes les préparations artisanales ou industrielles contenant des disaccharides (*Une lecture attentive des ingrédients est nécessaire*)	*Il peut y avoir du lactose dans les conservateurs ou du saccharose*
LAIT PRODUITS LAITIERS	⇨ Lait délactosé nature (Matin léger de lactel®) ⇨ Les boissons végétales SANS SUCRE et sans SOJA (ex : boisson à base d'avoine, de riz, d'amande, …) ⇨ Fromages à pâtes pressées (ex : comté, gruyère, mimolette, cheddar,…)	⇨ **TOUS les laits** de vache, brebis, jument, femme…. ⇨ Les Boissons à base de **soja** ⇨ **Tous les laitages** à base de lait de vache, brebis, …. ⇨ **Tous les fromages à pâtes molle** ou **fondu** (ex : chèvre, mozzarella, camembert, kiri®, vache qui rit®, …)	⇨ *Contiennent du lactose* ⇨ *Contiennent des oligosaccharides* ⇨ *Contiennent du lactose et du saccharose* ⇨ *Contiennent du lactose*
FECULENTS	• Pain blanc, complet, pâtes, semoule, riz, pomme de terre • Blé, tapioca • Biscottes SANS sucre • Farines blé, maïs, riz, … • Pâtisseries/biscuits FAIT MAISON en adaptant les ingrédients	• Pain de mie, pain viennois • Brioche, pain au lait, viennoiserie • Biscuits secs/moues • Pâtisseries • Pâtes brisées, sablés …. (*Une lecture attentive des ingrédients est nécessaire*)	*Contiennent du saccharose et +/- du lactose*
CEREALES	• **Céréales SANS lait ni saccharose** (ex : flocon d'avoine nature)	• **TOUS les céréales** contenant du sucre et/ou du lait (*Une lecture attentive des ingrédients est nécessaire*)	*Contiennent du saccharose et +/- du lactose*
LEGUMES LEGUMES SECS	• **TOUS les légumes** frais, en conserve ou surgelés **NATURE**	• Tous les légumes préparés contenant des disaccharides (*Une lecture attentive des ingrédients est nécessaire*) • Tous les produits à base de **soja (yaourt, crème, …)** • Tous les **légumes secs** (pois, haricots blanc – rouge, lentilles, pois chiche…)	*Contiennent du saccharose et/ou lactose* ⇨ *Contiennent des oligosaccharides* ⇨ *Contiennent des oligosaccharides*
FRUITS	• **TOUS les fruits** frais, en compote sans sucre ajouté ou surgelés non sucré • **TOUS les fruits secs** sans rajout de sucre • Les fruits oléagineux (cacahuète, pistache, noix, amande…)	• Les fruits au sirop, les compotes sucrées, ….	*Contiennent du saccharose*
SUCRES, PRODUITS SUCRES	• **Glucose** • **Fructose** • **Miel** • **Sirop 100% Agave** • Confiture sucrée au fructose • **Cacao pur** – chocolat NOIR sans SUCRE ni LAIT • Bonbons SANS sucre • Crème glacée/sorbet FAIT MAISON	• TOUS les sucres : poudre, morceaux, cassonnade, Candy, à base de canne, de betterave, d'érable …. • Caramel, bonbons divers, chocolat contenant du sucre et/ou du lait • Confitures, pâtes à tartiner avec lait /disaccharide • Sirop de fruit, boissons sucrées • Crème glacée, sorbet, glace à l'eau	*Contiennent du saccharose et +/- du lactose*
MATIERES GRASSES	• Toutes les huiles végétales (tournesol, colza, Isio 4, olive, …) • Toutes les margarines SANS lait • Crème de riz SANS sucre	• Beurre doux, demi-sel • Crème fraîche liquide – épaisse issu de lait animal	*Contiennent du lactose et +/- du saccharose*
BOISSON	⇨ Eaux plates, gazeuses ⇨ Tisanes, café, thé, ⇨ Jus de fruit 100% pur jus ⇨ Boissons SANS SUCRE (Zéro – light)	⇨ Eaux aromatisées avec sucre ⇨ Jus de fruit ou nectars de fruits sucrés ⇨ Boisson lactées, sucrées	⇨ *Contiennent du saccharose* ⇨ *Contiennent du saccharose* ⇨ *Contiennent du lactose et du saccharose*

N-acétyl-L-leucine (NALL)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of *N*-Acetyl-L-Leucine in Niemann–Pick Disease Type C

T. Bremova-Ertl, U. Ramaswami, M. Brands, T. Foltan, M. Gautschi, P. Gissen, F. Gowing, A. Hahn, S. Jones, R. Kay, M. Kolnikova, L. Arash-Kaps, T. Marquardt, E. Mengel, J.H. Park, S. Reichmannová, S.A. Schneider, S. Sivananthan, M. Walterfang, P. Wibawa, M. Strupp, and K. Martakis

- **N-acétyl-L-leucine (NALL)** est l'énantiomère L de la N-acétyl-DL-leucine -> Acide aminé modifié, dérivé de la L-leucine.
- Administration par voie orale, en 2 à 3 prises quotidiennes.
- Passage de la barrière hémato-encéphalique car transportée par les transporteurs de monocarboxylates (MCT), exprimés dans tous les tissus et donc dans tous les organes
- Mécanisme d'action encore incomplètement élucidé.
- Action sur les dysfonctionnements métaboliques et lysosomaux :

- Action sur les voies enzymatiques permettant de corriger les dysfonctionnements métaboliques et d'améliorer la production énergétique sous forme d'adénosine triphosphate (ATP)
- effets en cascade : les fonctions mitochondriales et lysosomales étant intrinsèquement liées, la normalisation du métabolisme énergétique permet d'améliorer le fonctionnement lysosomal et de réduire l'accumulation de cholestérol non estérifié et de sphingolipide
- La diminution des réserves en ATP entraîne une dépolarisation neuronale, responsable d'un dysfonctionnement des systèmes de transport ionique membranaire et d'une altération de l'excitabilité membranaire, perturbant ainsi la communication entre les neurones.
- Dans un modèle animal, il a été démontré que le traitement par NALL permettait de normaliser les potentiels membranaires neuronaux, ce qui pourrait améliorer les processus de signalisation cellulaire, restaurer les circuits neuronaux et les protéger.
- Dans différents modèles animaux, le traitement par NALL a également permis de réduire la neuro-inflammation, suggérant ainsi un **potentiel effet neuroprotecteur**



N-acétyl-L-leucine (NALL)

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N-acétyl-L-leucine : les premiers résultats chez l'animal



✓ Retard d'apparition des symptômes

✓ Amélioration des capacités motrices

✓ Ralentissement de la maladie

✓ Augmentation de la survie

- **Données précliniques**
- Dans un modèle murin Npc1−/− de la maladie de Niemann-Pick de type C, le traitement par NALL a permis :
- de retarder l'apparition du déclin fonctionnel (anomalies de la marche et troubles moteurs) ;
- de retarder la dégradation de l'état général, de la qualité du pelage et du poids corporel ;
- de ralentir la progression de la maladie ;
- de prolonger la survie.
- Ces effets ont été observés exclusivement avec l'énantiomère L et n'ont pas été retrouvés chez les animaux traités par N-acétyl-D-leucine.[5]
- Dans les modèles murins, le traitement par NALL a permis de réduire les troubles moteurs, l'ataxie et les troubles de la marche, qu'il soit instauré avant ou après l'apparition des symptômes.

- **Objectifs thérapeutiques :**
- Améliorer les manifestations neurologiques de la maladie.
- Ralentir la progression de la maladie à long terme.

Et chez l'homme?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of *N*-Acetyl-L-Leucine in Niemann–Pick Disease Type C

T. Bremova-Ertl, U. Ramaswami, M. Brands, T. Foltan, M. Gautschi, P. Gissen, F. Gowing, A. Hahn, S. Jones, R. Kay, M. Kolnikova, L. Arash-Kaps, T. Marquardt, E. Mengel, J.H. Park, S. Reichmannová, S.A. Schneider, S. Sivananthan, M. Walterfang, P. Wibawa, M. Strupp, and K. Martakis

60	5–67	3 mois
patients	ans	de traitement actif

Évaluation des capacités neurologiques

Marche · Équilibre · Coordination · Parole

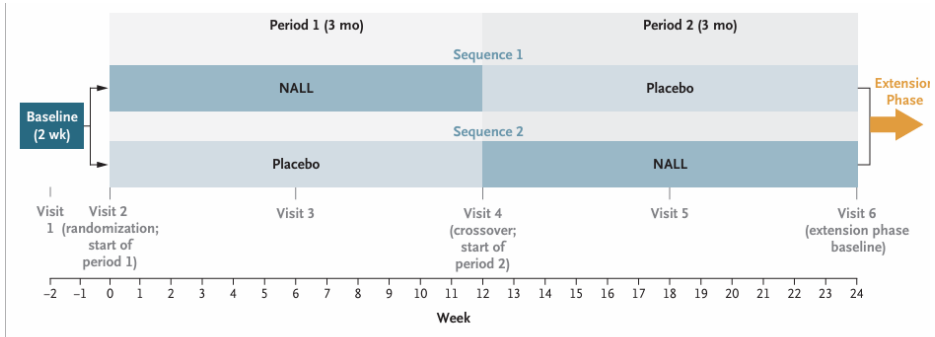

Figure 1. Trial Design.
The patients were randomly assigned in a 1:1 ratio to receive *N*-acetyl-L-leucine (NALL) for 12 weeks in period 1, followed by placebo for 12 weeks in period 2 (sequence 1), or to receive placebo for 12 weeks in period 1, followed by NALL for 12 weeks in period 2 (sequence 2). NALL or placebo was immediately switched at the end of period 1 (visit 4).

Dose group — no. (%)	
Age 4 to 12 yr	
15 to <25 kg of body weight: 2 g per day	6 (10)
25 to <35 kg of body weight: 3 g per day	3 (5)
25 to ≥35 kg of body weight: 4 g per day	3 (5)
Age ≥13 yr: 4 g per day	48 (80)
Miglustat use — no. (%)§	51 (85)

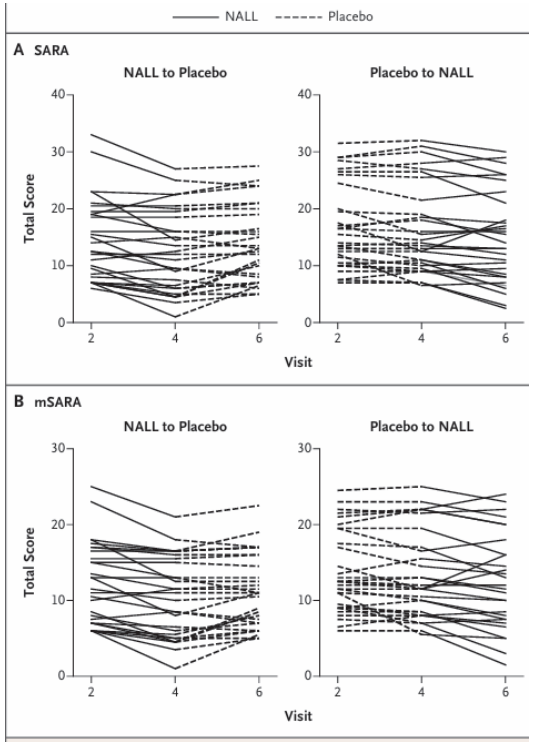

Figure 2. SARA and mSARA Total Scores at Visits 2, 4, and 6.
Shown are the total scores on the Scale for the Assessment and Rating of Ataxia (SARA; Panel A) and the modified SARA (mSARA; Panel B) for the individual patients at visits 2, 4, and 6 according to active treatment–placebo treatment. Total scores on the SARA range from 0 to 40, and total scores on the mSARA range from 0 to 30; on both scales, lower scores indicate better neurologic status.

SAFETY

The adverse events that occurred during the two treatment periods are shown in Table S4. A total of 79 adverse events occurred in 36 patients when they were receiving NALL, and 75 events occurred in 30 patients when they were receiving placebo. No adverse events led to premature discontinuation of the trial. No adverse events occurred in more than 10% of patients when they were receiving NALL. Three patients each had 1 adverse event that was assessed by the investigator to be related to NALL (anal incontinence, restless legs, and rosacea). These events were all transient. The incidence of upper respiratory tract infection was higher when the patients were receiving NALL (10%) than when they were receiving placebo (5%). The incidence of falls was lower when the patients were receiving NALL (7%) than when they were receiving placebo (15%). Epilepsy, which is a feature of Niemann–Pick disease type C, occurred once when a patient was receiving NALL.

No serious adverse events occurred that were considered by an investigator to be related to NALL or placebo. One death was due to aspiration pneumonia after a preplanned placement of a percutaneous endoscopic gastrostomy tube and therefore was not related to trial treatment. The results of plasma and urine tests, vital signs, and electrocardiographic recordings were normal or were rated as clinically nonsignificant. Adherence to NALL or placebo was high, as shown by the results of regular urine analyses for prohibited medications.

NALL au long cours

RESEARCH ARTICLE OPEN ACCESS

Disease-Modifying, Neuroprotective Effect of N-Acetyl-L-Leucine in Adult and Pediatric Patients With Niemann-Pick Disease Type C

Marc C. Patterson,[1] Uma Ramaswami,[2] Aimee Donald,[3] Tomas Foltan,[4] Matthias Gautschi,[5] Paul Gissen,[6] Andreas Hahn,[7] Simon A. Jones,[3] Richard Kay,[8] Miriam Kolniková,[4] Julien Park,[9] Stella Reichmannová,[10] Mark Walterfang,[11] Pierre Wibawa,[11] Marianne Rohrbach,[12] Kyriakos Martakis,[7,13,*] and Tatiana Bremova-Ertl[5,*]

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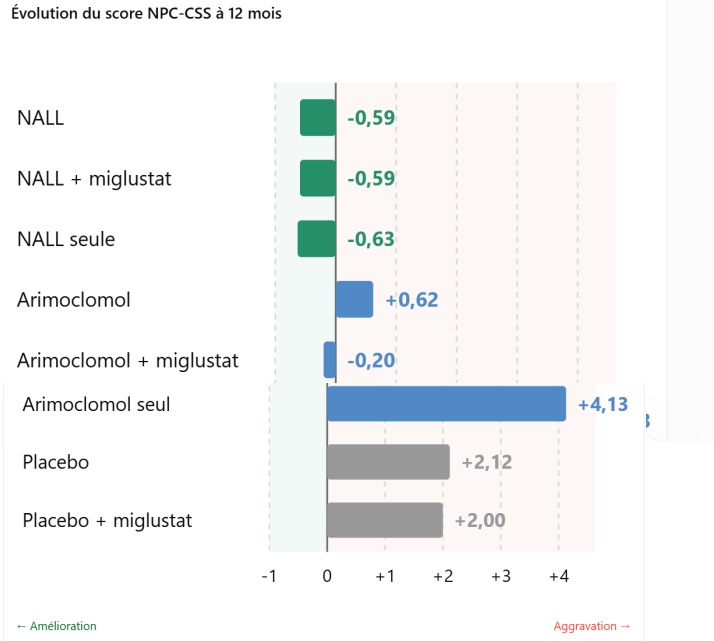
Neurology® 2025;105:e213589. doi:10.1212/WNL.0000000000213589

Table 3 Comparison of the 4-Domain NPC-CSS Scores While Receiving NALL With Those of Clinical Trial Cohorts

	12 mo from baseline		
Cohort	**n**	**Mean change from baseline[a]**	**Mean difference vs IB1001-301 EP cohort (NALL)**
IB1001-301 extension phase cohort (NALL)[b]	49	−0.59 (SD = 1.79)	N/A
Patients on NALL + miglustat	41	−0.59 (SD = 1.86)	N/A
Patients on NALL (no miglustat)	8	−0.63 (SD = 1.51)	N/A
Arimoclomol-treated cohort (from arimoclomol phase II/III trial)[19,c]	34	+0.62 (SD = 0.39)	+1.21
Patients on arimoclomol + miglustat[9]	22	−0.2 (SD = 1)	+0.39
Patients on arimoclomol (no miglustat)[19]	8	+4.13 (N/A)	+4.27
Placebo-treated cohort (from arimoclomol phase II/III trial)[19,d]	16	+2.12 (SD = 0.59)	+2.71
Patients on placebo + miglustat[9]	12	+2.0 (SD = 0.7)	+2.59
Patients on placebo (no miglustat)[19]	3	+1.98 (N/A)	+2.57

Abbreviations: EP = extension phase; NALL = N-acetyl-L-leucine; NPC-CSS = Niemann-Pick disease type C Clinical Severity Scale.
[a] A higher score represents disease worsening; a lower score reflects disease improvement.
[b] Includes patients treated with NALL (no miglustat) (n = 8) and patients treated with NALL + miglustat (n = 41).
[c] Includes patients treated with arimoclomol (no miglustat) (n = 8) and patients treated with arimoclomol + miglustat combination therapy (n = 26).
[d] Includes patients treated with placebo (no miglustat) (n = 4) and placebo + miglustat (n = 12).



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GENERAL NEUROLOGY: PHARMACEUTICALS | June 10, 2026 | Check for updates

Long-Term 30-Month Results of N-Acetyl-L-Leucine for Niemann-Pick Disease Type C (P11-7.003)

Michael Strupp, Marc Patterson, Bethany Zanrucha, Janelle Raymond, Asante Hatcher, Jorgji Kerthi, Taylor Fields, Ian Billington, and Tatiana Bremova-Ertl AUTHORS INFO & AFFILIATIONS

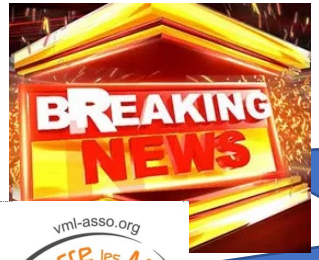
June 9, 2026 issue • 106 (11_Supplement_1) 3239 • https://doi.org/10.1212/WNL.0000000000216341

Results

Fifty-four participants aged 5 to 67 years were treated in the EP. The interim 24-month mean (±SD) change from baseline on the 5-domain NPC-CSS was −0.32 (±2.66) on NALL, i.e., improvement, compared to 3.0 (±6.32) in the historical cohort: mean difference −3.32. Results of the 15-domain NPC-CSS were supportive of the primary analysis and improvements in neurological status as measured by SARA were sustained over the 24-month follow-up. No drug-related TEAEs, SAEs, or deaths occurred during the study. Long-term 30-month data will be presented at the 2026 American Academy of Neurology pending data availability.

Conclusions

Long-term 24-month treatment with NALL has demonstrated statistically significant and clinically meaningful reduction in disease progression.



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Vaincre les Maladies Lysosomales
RARE MAIS PAS SEUL !

Données présentées lors du congrès Child Neurology Society (oct 2026, Montréal) sur 39 patients (enfants + adultes) à 36 mois de phase d'extension: stabilisation de l'état neurologique (comparaison avec histoire naturelle, pas contre placebo) : progression maladie hist nat 4,5point/3a, patients traités amélioration 0,28point

U.S. FOOD & DRUG ADMINISTRATION

Home / News & Events / FDA Newsroom / Press Announcements / FDA Approves New Drug to Treat Niemann-Pick Disease, Type C

FDA NEWS RELEASE

FDA Approves New Drug to Treat Niemann-Pick Disease, Type C

More Press Announcements

For Immediate Release: September 24, 2024

Today, the U.S. Food and Drug Administration approved Aqneursa (levacetylleucine) for the treatment of neurological symptoms associated with Niemann-Pick disease type C (NPC) in adults and pediatric patients weighing at least 15 kilograms.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 November 2025 Rev. 2[1]
EMA/114031/2025
Committee for Medicinal Products for Human Use (CHMP)

Summary of opinion[2] (initial authorisation)

Aqneursa

levacetylleucine

On 24 July 2025, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Aqneursa[3], intended for the treatment of neurological manifestations of Niemann-Pick Type C (NPC) disease in adults and children from 6 years of age weighing at least 20 kg. The CHMP also concluded that the active substance, levacetylleucine, could not be considered a new active substance; this conclusion was confirmed on 13 November 2025 after re-examination of the initial opinion.

Indication	Manifestations neurologiques du NPC	Manifestations neurologiques du NPC
Âge minimal	Pas de seuil spécifié	6 ans
Poids minimal	15 kg	20 kg
Association au miglustat	Non obligatoire	Obligatoire sauf intolérance
Monothérapie possible	Oui	Uniquement si intolérance au miglustat
Posologie	2 à 4 g/j	2 à 4 g/j
Prise alimentaire	Avec ou sans repas	À distance des repas

Hydroxypropyl-β-cyclodextrine (HPβCD)

NIH Public Access
Author Manuscript
Clin Lipidol. Author manuscript; available in PMC 2014 August 20.

Published in final edited form as:
Clin Lipidol. 2012 June ; 7(3): 289–301. doi:10.2217/clp.12.31.

Therapeutic potential of cyclodextrins in the treatment of Niemann–Pick type C disease

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Niemann-Pick type C disease: molecular mechanisms and potential therapeutic approaches

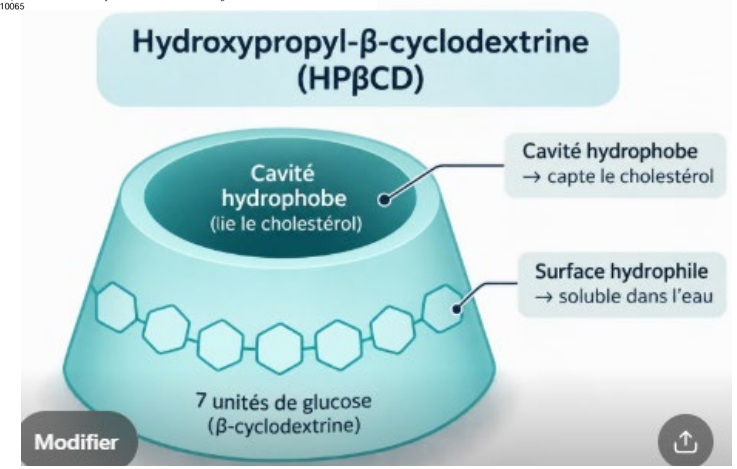
Anton I. Rosenbaum and **Frederick R. Maxfield**
Department of Biochemistry, Weill Cornell Medical College, 1300 York Avenue, New York, NY 10065

thematic review

Thematic Review Series: Recent Advances in the Treatment of Lysosomal Storage Diseases

Niemann-Pick C disease and mobilization of lysosomal cholesterol by cyclodextrin

Jean E. Vance[1,*] and Barbara Karten[1]



- oligosaccharides cycliques naturellement présents, obtenus par conversion enzymatique de l'amidon
- structure toroïdale creuse, en forme de cône tronqué, avec une cavité hydrophobe et une surface extérieure hydrophile
- Grande compétence du 2HPβCD à se lier au cholestérol (piégeage ou navette de cholesterol)
- Utilisation IV chez la jeune souris (7j):

- Doublement de la durée de vie.

- Diminution de l'accumulation neuronale de cholestérol et de glycosphingolipides.

- Normalisation du contenu en cholestérol dans presque tous les organes.

- Réduction du stock total de cholestérol de l'organisme jusqu'à des valeurs pratiquement normales

- Doute sur le passage de la BHE dans la sourie (passage faible)

Hydroxypropyl-β-cyclodextrine (HPβCD) IV

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Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

Long-term administration of intravenous Trappsol® Cyclo™ (HP-β-CD) results in clinical benefits and stabilization or slowing of disease progression in patients with Niemann-Pick disease type C1: Results of an international 48-week Phase I/II trial

Reena Sharma[a,1], Caroline Hastings[b,*,1], Orna Staretz-Chacham[c], Julian Raiman[d], Martin Paucar[e], Ronen Spiegel[f,g], Bryan Murray[h], Bryan Hurst[h], Benny Liu[i], Lise Kjems[i], Sharon Hrynkow[i]

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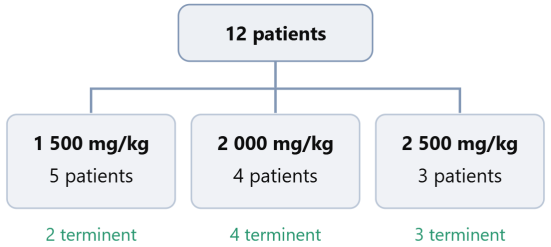
[j] Cyclo Therapeutics, Inc, 6714 NW 16th Street, Suite B, Gainesville, FL 32653, USA

Étude multicentrique internationale de phase I/II, randomisée, en double aveugle, menée dans cinq centres (Royaume-Uni, Suède et Israël).

Patients inclus	Âge des patients
12	2–39 ans
Durée de traitement	**Patients sous miglustat**
48 semaines	10/12

Trois groupes de traitement



Une perfusion toutes les deux semaines
Durée de perfusion : 8 à 9 heures

8/9 Amélioration d'au moins deux domaines du NPC-CSS

6/9 Amélioration d'au moins un domaine essentiel à la qualité de vie

7/9 Amélioration clinique globale selon le médecin

Résultats parmi les neuf patients ayant terminé l'étude.

Les cinq domaines considérés comme essentiels à la qualité de vie des patients et des familles étaient la marche, la motricité fine, la parole, la déglutition et la cognition.

Table 4
17D-NPC-CSS domains showing improvement or worsening at end of study.

Patient Number (age, years)	Improvement in Individual Domains at Week 48 compared with baseline	Worsening in Individual Domains at Week 48 compared with baseline	NPCSS Total at baseline	NPCSS Total at Week 48 or end of study
2 (21)	**Swallow − 1** Seizures −2 Gelastic Cataplexy −1 Incontinence −1	**Fine Motor Skills + 1** **Cognition + 1**	**24**	**21**
3 (39)	Eye Movement −1 **Fine Motor Skills − 1** Psychiatric −1	None	12	9
5 (4)	Gelastic Cataplexy-1 Auditory brainstem response −1 Memory −1	None	24	21
6 (11)	**Ambulation − 1** **Swallow − 2** Gelastic Cataplexy −2 Hyperreflexia −1 Narcolepsy −1 Incontinence-1 Behavior −1	**Speech + 1** **Fine Motor Skills + 2** Hearing +2	**26**	**22**
7 (2)	**Ambulation − 3** **Fine Motor Skills − 1**	**Speech + 1** Hyperreflexia +1	**5**	**3**
8 (3)	Eye Movement −1 **Speech-1**	**Fine Motor Skills + 1** Hearing +2	**16**	**17**
10 (2)	None	**Cognition + 2** **Fine Motor Skills + 1** Hyperreflexia +1	**15**	**19**
11 (2)	Eye Movement −1 **Cognition − 2**	**Fine Motor Skills + 1** Memory +1	**9**	**8**
12 (8)	Gelastic Cataplexy −1 Incontinence −1	**Ambulation + 1** **Fine Motor Skills + 1** Memory +2 Hyperreflexia +1	**13**	**16**

Patient 1 withdrawn at Week 24, Patient 4 no consent for 17D-NPC-CSS, Patient 9 unable to attend Week 48 due to COVID-19.
Domains in **bold** text are those determined by NPC families and their caregivers, in collaboration with the FDA [44], to be the most important for quality of life.

- Passage de la cyclodextrine dans le LCR dès H4 de la fin de la perfusion (donc H13 du début)(sauf pour 1 patient/12)
- Diminution des précurseurs du cholestérol dans le sérum et augmentation des métabolites du cholestérol, résultat évocateurs de la libération du cholestérol auparavant enclavé dans les lysosomes
- Diminution du biomarqueur PCCS dans le sang et de la protéine tau dans le LCR
- Surveillance de l'ototoxicité (5 ont eu une atteinte auditive dont 2 permanentes, non ressenties par les patients)

Hydroxypropyl-β-cyclodextrine (HPβCD) IT

Intrathecal 2-hydroxypropyl-β-cyclodextrin decreases neurological disease progression in Niemann-Pick disease, type C1: a non-randomised, open-label, phase 1–2 trial

Daniel S Ory, Elizabeth A Ottinger, Nicole Yanjanin Farhat*, Kelly A King, Xuntian Jiang, Lisa Weissfeld, Elizabeth Berry-Kravis, Cristin D Davidson, Simona Bianconi, Lee Ann Keener, Ravichandran Rao, Ariane Soldatos, Rohini Sidhu, Kimberly A Walters, Xin Xu, Audrey Thurm, Beth Solomon, William J Pavan, Bernardus N Machielse, Mark Kao, Steven A Silber, John C McKew, Carmen C Brewer, Charles H Vite, Steven U Walkley, Christopher P Austin, Forbes D Porter*

14 patients inclus de 2013 à 2015

3 patients 50mg IT/mois

3 patients 200mg IT/mois

3 patients 300mg IT/mois

3 patients 400mg IT/mois

2 patients 900mg IT/mois

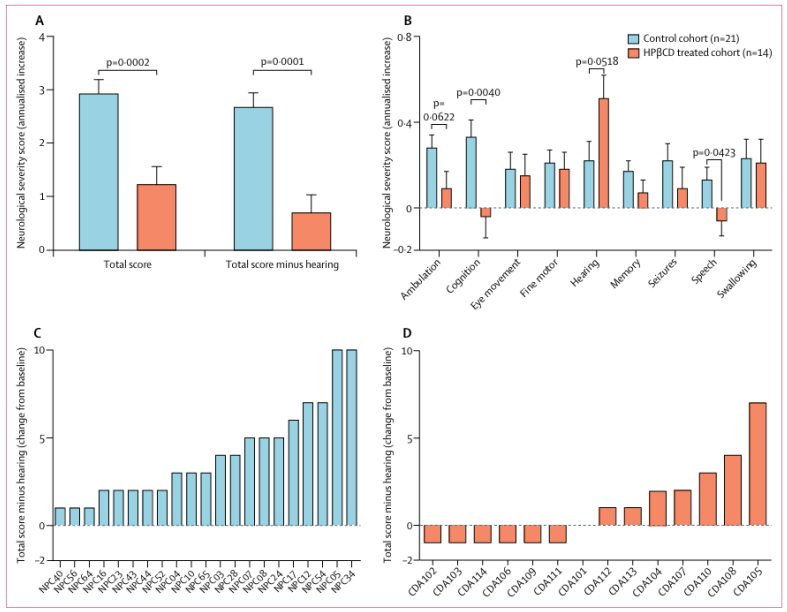


Figure 6: **Clinical efficacy of intrathecal HPβCD**
NNSS=NPC Neurological Severity Score. NPC1=Niemann-Pick disease, type C1. HPβCD=2-hydroxypropyl-β-cyclodextrins.NNSS was used to characterise NPC1 disease progression in 21 control patients (blue bars) and 14 HPβCD-treated participants (red bars). (A) Annualised rate of disease progression, as ascertained by the total NNSS and total NNSS minus hearing components, in HPβCD-treated participants compared with the control patients. Data are from the 12-month assessment for

- Résultats négatifs
- Beaucoup d'effets indésirables
- Le laboratoire annonce l'arrêt des protocoles de recherche en 2021

ClinicalTrials.gov

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The U.S. government does not review or approve tl

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VTS-270 to Treat Niemann-Pick Type C1 (NPC1) Disease

Arm/Group Title	Part A: Adrabetadex 900 mg	Part A: Adrabetadex 1200 mg	Part A: Adrabetadex 1800 mg	Part A: Sham Control	Part B: Adrabetadex 900 mg	Part B: Sham Control
Arm/Group Description	Participants received 4 lumbar intrathecal (IT) infusions of adrabetadex 900 milligrams (mg) once every 2 weeks.	Participants received 4 lumbar IT infusions of adrabetadex 1200 mg once every 2 weeks.	Participants received 4 lumbar IT infusions of adrabetadex 1800 mg once every 2 weeks.	Participants received sham control procedures once every 2 weeks.	Participants received lumbar IT infusions of adrabetadex 900 mg once every 2 weeks.	Participants received sham control procedures once every 2 weeks.

biomedicines

MDPI

Systematic Review

Therapeutic Interventions in Niemann–Pick Disease Type C: A Systematic Review of Clinical Outcomes and Safety

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Table 7. Studies retrieved from the ClinicalTrials.gov.

S.NO	STUDY TITLE	INTERVENTIONS & COMPARATOR	POPULATION DEMOGRAPHICS	PRIMARY OUTCOMES	RESULTS	ADVERSE EVENTS
1.	A Phase 2b/3 Prospective, Randomized, Double-Blind, Sham-Controlled 3-Part Trial of VTS-270 (2-hydroxypropyl-β-cyclodextrin) in Subjects With Neurologic Manifestations of Niemann–Pick Type C1 (NPC1) Disease [24] **Study design**: Randomized, double-blind, sham-controlled Parts A/B; NCT02534844	**Intervention:** HPβCD (Adrabetadex/VTS-270) (n = 38) **Comparator**: Sham control (n = 18)	**Age**: 4–21 years **Sex**: 30 male/26 female	Change in 4-Item Composite NPC-SS Score (Week 52)	Four-item NPC-SS change was -0.1 ± 1.55 with sham versus 0.0 ± 2.45 with adrabetadex. CGIC responders were 7/18 versus 23/38; NPC-SS responders were 13/18 versus 22/38. Median time to worsening was 118 versus 169 days. No comparative *p*-values were posted.	Treatment-emergent AEs occurred in 17/18 (94.4%) versus 37/38 (97.4%); serious AEs in 3/18 (16.7%) versus 19/38 (50.0%). One death occurred in each group.
2.	A Phase 2b/3 Prospective, Randomized, Double-blind, Sham-controlled Trial of VTS-270 (2-hydroxypropyl-β-cyclodextrin) in Subjects with Neurologic Manifestations of Niemann–Pick Type C1 (NPC1) Disease [25] **Study design:** Open-label Part C continuation; NCT04958642	**Intervention:** HPβCD (Adrabetadex) (n = 66) **Comparator**: None	**Age**: 4–21 years **Sex**: 34 male/32 female	Participants experiencing treatment-emergent AEs or serious AEs over ≤5 years	Treatment-emergent AEs occurred in 18/18 treatment-naïve, 13/13 Phase I, and 34/35 Parts A/B participants: overall 65/66 (98.5%). Serious AEs occurred in 9/18, 7/13, and 20/35, respectively: overall 36/66 (54.5%).	Two deaths occurred: one treatment-naïve participant and one Parts A/B continuation participant. Reported serious events included infections, respiratory failure, seizures, procedural complications, hemorrhage, and hearing disorders.
3.	A Phase 2b/3 Open-label Trial of VTS-270 (2-hydroxypropyl-β-cyclodextrin) in Subjects With Neurologic Manifestations of Niemann–Pick Type C1 Disease Previously Treated Under Protocol VTS301 [26]	**Intervention:** HPβCD (Adrabetadex) (n = 2) **Comparator**: None	**Age**: <18 years **Sex**: Not reported	Participants experiencing treatment-emergent AEs or serious AEs through Week 156	Both participants experienced treatment-emergent AEs; neither experienced a serious AE.	No deaths; no SAEs reported
4.	Open-label Evaluation of Adrabetadex in Patients with Neurologic Manifestations of Niemann–Pick Type C Disease (NPC) [27] Study design: Open-label, Interventional; NCT03643562	**Intervention:** HPβCD (Adrabetadex) (n = 27) **Comparator**: None	**Age**: 16–21 years **Sex**: 16 male/11 female	Participants experiencing treatment-emergent AEs or serious AEs through Week 134	Treatment-emergent AEs occurred in 9/9 treatment-naïve and 17/18 previously treated participants: overall 26/27 (96.3%). Serious AEs occurred in 5/9 and 9/18, respectively: overall 14/27 (51.9%).	Ventricular extrasystoles, Deafness, Constipation

Efficacy of Intrathecal Adrabetadex in Infantile-Onset Niemann-Pick Disease Type C is Supported by Survival, Clinical, and Biomarker Data

IR015

Forbes D. Porter, MD, PhD[1]; Laurence H. Keller, MD[2]; Lixia Jiao, PhD[2]; John P. Winnike, MS[2]; Alexander M. Gold, MD[2]; Jason Camm[2]; Elizabeth Berry-Kravis, MD, PhD[1]

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BACKGROUND

Disease Overview

- Niemann-pick disease type C (NPC) is a rare genetic disorder that impairs intracellular cholesterol trafficking, leading to progressive neurological decline and premature death[1-3]
- NPC subtype is classified based on age of neurological symptom onset, with infantile onset (<6 years of age) (I-NPC) being associated with the most severe phenotype and rapid rate of disease progression[1,2,4]

NPC Standard of Care and Measuring Disease Progression

- Usual care for NPC has historically involved management of symptoms, with no cure and limited impact on survival. Miglustat, although only approved by the European Medicines Agency (EMA), is commonly used off label in the United States and considered part of routine management[2,5]
- Disease progression can be assessed using a short-form NPC Clinical Severity Scale (Revised 4-Domain NPC Clinical Severity Scale [R4DNPCCSS]), which evaluates ambulation, speech, fine-motor function, and swallowing[6]

Biomarkers Related to NPC1 Neuropathology are Linked to[3]:

- Underlying disease pathology
  - 24(S)-OHC: primary route for excess brain cholesterol[6]
- Neurodegeneration
  - Calbindin D: calcium-binding protein enriched in Purkinje neurons[7]
  - FABP3: cytosolic protein involved in membrane dynamics and synapse formation[8]

Adrabetadex Investigational Therapy

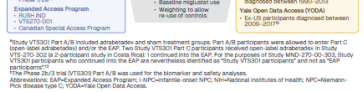
- Adrabetadex is a well-characterized 2-hydroxypropyl-β-cyclodextrin (HPβCD) mixture suitable for intrathecal (IT) administration that targets the underlying pathology of NPC by re-establishing cholesterol trafficking[9-12]
- We report overall survival (OS) among individuals with I-NPC treated with investigational drug adrabetadex compared with external controls, and evaluate long-term disease progression in treated individuals

METHODS

Survival and NPC-CSS Outcomes and Analysis (Figure 1)

- The primary objective was to compare OS (baseline to death or last known alive) in patients with early and late I-NPC treated with adrabetadex vs external controls receiving usual care
- Match-eligible adrabetadex-treated participants had early or late I-NPC and received ≥ dose of adrabetadex. Adrabetadex was administered intrathecally via lumbar puncture at doses of 50–1200 mg every 4 weeks (Q4W) in Phase 1/2a and 900–1800 mg every 2 weeks (Q2W) in VTS301 Part A; 900 mg Q2W was selected as the recommended regimen for VTS301 Parts B and C. Dose reduction was allowed to manage tolerability. In the Expanded Access Programs (EAPs), participants started at 200 or 400 mg (depending on age) Q2W with titration up to 1200 mg (initially) or 900 mg (later revision)
- OS was compared with matched external controls from 4 major disease databases or publications[3,13-15] OS analysis cutoff was January 10, 2025
- Hazard ratios (HR) with 95% confidence intervals (CI) were calculated using a weight-adjusted Cox regression model including treatment (adrabetadex–treated vs matched controls) as fixed effect, and history of miglustat as a covariate
- Log-rank P-values were calculated using a weight-adjusted Kaplan-Meier (KM) analysis. Subgroup OS analyses included baseline miglustat use and participants with early and late I-NPC
- The annual rate of clinical disease progression assessed by R4DNPCCSS during adrabetadex treatment was compared with pretreatment periods. A longitudinal mixed effects model estimated mean annual rates of change pre- and post–adrabetadex treatment, with R4DNPCCSS scores imputed as 0 at birth to anchor trajectories

Figure 1. Data Sources for Survival Analysis



*Study VTS301 Part A/B included adrabetadex and sham treatment groups. Part A/B participants were allowed to enter Part C (open-label adrabetadex) and/or the EAP. Two Study VTS301 Part C participants received open-label adrabetadex in Study VTS-270-302 (a 2 participant study in Costa Rica). I continued into the EAP. For the purposes of Study MND-270-00-303, Study VTS301 Part C participants who continued into the EAP are nevertheless identified as "Study VTS301 participants" and not as "EAP participants"[12].

†The Phase 2b/3 trial (VTS301 Part A/B was used for the biomarker and safety analyses.

Abbreviations: EAP=Expanded Access Program; I-NPC=infantile-onset NPC; NIH=National Institutes of Health; NPC=Niemann-Pick disease type C; YODA=Yale Open Data Access.

Biomarker Analysis

- Cerebrospinal fluid (CSF) levels of 24(S)-OHC, calbindin D, and FABP3 were measured in participants from the Phase 2b/3 trial (VTS301 Part A/B (**Supplemental Figure 1**). Wilcoxon signed-rank test was used to assess within-group changes in CSF biomarkers from baseline to Week 52 (SAS v9.4). Nominal statistical significance was defined as $P < 0.05$ without adjustment for multiplicity. See Supplemental methods for more details.

Safety

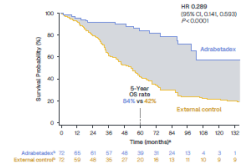
- Results are reported from the Phase 2b/3 trial (VTS301) Part A/B safety population, defined as all randomized subjects who received ≥1 procedure (IT adrabetadex or sham). See Supplemental results for more details.

RESULTS

Overall Survival

- Of 80 total participants treated with adrabetadex eligible for matching, 72 (32 early infantile; 40 late infantile) were successfully matched, with a median treatment duration of 3.8 years (range 0.1–11 years).
- Of the pooled 255 I-NPC external controls eligible for matching, 119 (57 early infantile; 62 late infantile) were successfully matched
- Baseline demographic and clinical characteristics were generally comparable between the 2 groups (**Table 1**)
- Participants treated with adrabetadex had a significantly reduced risk of death compared with external control individuals (**Figure 2**)
- The OS benefit was seen in participants treated with miglustat and not treated with miglustat at baseline (**Figure 3; Supplemental Figure 2**)
- Survival benefit was consistent for early and late I-NPC, as well as for comparisons to each individual external control cohort (**Figure 3; Supplemental Figure 3**)

Figure 2. OS in Matched Participants With I-NPC



*KM curves are visually truncated at ~132 months. †Weighted numbers at risk are shown for external control individuals to account for the many-to-1 matching to treated patients.

Abbreviations: HR=hazard ratio; KM=Kaplan-Meier; OS=overall survival.

Table 1. Baseline Demographics and Disease Characteristics

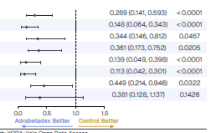
	Adrabetadex (N=72)	External Control (N=119)
Age at onset category, n/N (%)		
<2 Years	32/72 (44)	57/119 (48)
2–<6 Years	40/72 (56)	62/119 (52)
Median age at neurological onset, months (Q1, Q3)	25 (0, 68)	24 (0, 68)
Overall miglustat use, n/N (%)	52/72 (72)	72/119 (61)
G-tube, n/N (%)*	11/50 (22)	6/26 (23)
Respiratory therapy, n/N (%)	17/50 (18)	2/26 (8)
Race, n/N (%)*		
White	65/72 (90)	22/26 (85)
Other	7/72 (10)	4/26 (15)
Region, n/N (%)*		
Europe	11/72 (15)	90/119 (76)
North America	61/72 (85)	27/119 (23)
South America	0 (0)	2/119 (2)

*Comparability factors were not available from all sources.

Abbreviations: G-tube=gastrostomy tube; Q1=first quartile; Q3=third quartile.

Figure 3. OS by Subgroups and Individual External Control Cohorts

Population and comparator source	Number of Deaths (%)		HR (95% CI)	*P* Value
	Adrabetadex	External Control		
Overall infantile	17 (23.6%)	44 (61.2%)	0.289 (0.141, 0.593)	<0.0001
Early infantile	9 (28.1%)	24 (75.1%)	0.148 (0.064, 0.343)	<0.0001
Late infantile	8 (20.0%)	20 (49.2%)	0.344 (0.146, 0.812)	0.0457
With miglustat	8 (22.9%)	13 (37.9%)	0.361 (0.173, 0.752)	0.0205
Without miglustat	7 (33.3%)	19 (91.2%)	0.139 (0.049, 0.398)	<0.0001
French comparator	9 (16.4%)	44 (80.7%)	0.113 (0.042, 0.301)	<0.0001
NIH comparator	12 (33.3%)	30 (84.2%)	0.449 (0.214, 0.946)	0.0322
YODA comparator	8 (21.6%)	6 (16.4%)	0.391 (0.129, 1.137)	0.1426

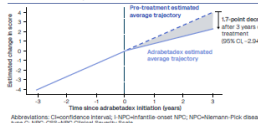


Abbreviations: HR=hazard ratio; OS=overall survival; NIH=National Institutes of Health; YODA=Yale Open Data Access.

Disease Progression by NPC Clinical Severity Scores

- 79 treated participants contributed R4DNPCCSS scores. Adrabetadex treatment significantly reduced the annual rate of disease progression from 1.34 units/year before treatment to 0.76 units/year after treatment (difference 0.58 units/year; 95% CI, −0.98 to −0.18; $P = 0.0055$; **Supplemental Table 1**), reflecting a 43% reduction in the annual rate of progression
- The mean estimated difference between treated and untreated trajectories of R4DNPCCSS scores after 3 years of adrabetadex treatment was −1.7 (95% CI, −2.94 to −0.53), illustrating a meaningful decrease in R4DNPCCSS scores in participants treated with adrabetadex (**Figure 4**).

Figure 4. Longitudinal Disease Progression Analysis Using Short Form NPC-CSS in Participants With I-NPC

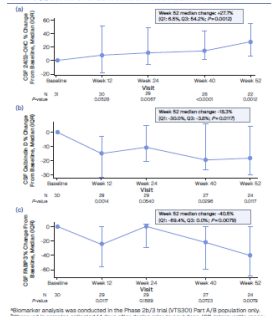


Abbreviations: CI=confidence interval; I-NPC=infantile-onset NPC; NPC=Niemann-Pick disease type C; NPC-CSS=NPC Clinical Severity Scale.

Biomarker Analysis

- Baseline demographics and clinical characteristics were generally comparable between the 2 groups (**Supplemental Table 2**)
- CSF 24(S)-OHC levels increased by 21.7% after 52 weeks of IT adrabetadex treatment (n=22; $P = 0.0012$; **Figure 5a**)
- Adrabetadex–treatment was associated with decreases in CSF calbindin-D levels (15.3%; n=24; $P = 0.0017$; **Figure 5b**), and FABP3 (40.5%; n=24; $P = 0.0078$; **Figure 5c**)

Figure 5. Percent Change in CSF 24(S)-OHC (a), Calbindin D (b), and FABP3 (c) Levels Over 52 Weeks of Adrabetadex Treatment[a,b]



[a]Biomarker analysis was conducted in the Phase 2b/3 trial (VTS301) Part A/B population only. [b]Observed in samples collected 14 days after dosing prior to next dose. IQR, interquartile range; Q1, first quartile; Q3, third quartile.

CONCLUSIONS

- Adrabetadex treatment **substantially improves survival** in individuals with I-NPC compared with matched external controls
- Survival benefit was **consistent for early and late I-NPC and regardless of miglustat use at baseline**
- Treatment is associated with a **43% reduction in the annual rate of neurologic disease progression**
- Biomarker findings are consistent with and build on preclinical research and early clinical studies of adrabetadex
  - Biomarker changes were observed 14 days after dosing, demonstrating a prolonged central nervous system (CNS) effect despite adrabetadex's short CSF half-life (~6.6 hours)[16]
  - Statistically significant CSF increase of 24(S)-OHC indicate that adrabetadex **targets the underlying pathology of NPC1 by re-establishing neuronal intracellular cholesterol trafficking**
  - Decreased CSF levels of calbindin D and FABP3 suggest that adrabetadex **decreases neuronal damage and cell death**
- These findings support that adrabetadex is an important investigational drug with potential as a disease modifying therapy to improve clinical outcomes in individuals with I-NPC

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Efficacy of Intrathecal Adrabetadex in Infantile-Onset Niemann-Pick Disease Type C is Supported by Survival, Clinical, and Biomarker Data

IR015

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SUPPLEMENTAL METHODS

Biomarker Analysis

- Analyses included participants from the Phase 2b/3 trial (VTS301) Part A/B (**Supplemental Figure 1**).
- VTS301 was a Phase 2b/3, randomized, double-blind, sham-controlled trial evaluating the effect of intrathecal (IT) adrabetadex in NPC1 participants with onset of neurologic manifestations before age 15. The trial was composed of 3 parts: Part A (dose finding) and Part B (sham-controlled): NCT02534844; Part C (open-label extension): NCT04956542, which included participants from Parts A/B and from the Phase 1/2a study (NCT01747135). IT adrabetadex 900 mg was administered once every 2 weeks (Q2W); dose reduction was allowed for tolerability
- Biomarker assays were validated for sensitivity, precision, and reproducibility according to US Food and Drug Administration (FDA) guidelines
- CSF levels of 24(S)-OHC were quantified using an oxysterol assay gas chromatography–mass spectrometry selected ion monitoring protocol developed at the laboratory of Dr Dieter Lütjohann (University of Bonn, Germany).[1] CSF levels of calbindin D and FABP3 were measured with Quanterix® Immunoassays at Rules-Based Medicine (RQVIA, Austin, TX).
- Wilcoxon signed-rank test was used to assess within-group changes in CSF biomarkers from baseline to Week 52 (SAS v9.4). Nominal statistical significance was defined as $P < 0.05$ without adjustment for multiplicity.

Supplemental Figure 1. Phase 2b/3 Trial (VTS301) Study Design



*Dose reduction permitted for tolerability. †Rescue option in study design allowed participants to transfer from sham arm to Part C at 6 months with disease progression. BL, baseline; Q2W, once every 2 weeks; R, randomization.

Abbreviations: BL=baseline; CSF=cerebrospinal fluid; IT=intrathecal; NPC=Niemann-Pick disease type C; Q2W=once every 2 weeks; R=randomization.

SUPPLEMENTAL RESULTS

Supplemental Table 1. Annual Rate of Change in Short Form NPC-CSS Score During the Untreated and Treatment Periods in Participants With I-NPC

	Infantile-Onset
Participants, n	79
Pre-treatment visits, n	337
Treatment visits, n	689
Annual change in score (units/year), estimate (95% CI)	
Pre-treatment periods	1.34 (0.98, 1.71)
Treatment periods	0.76 (0.52, 1.01)
Treatment – pre-treatment	−0.58 (−0.98, −0.18)
P-value for difference	0.0055

Supplemental Table 2. Baseline Demographics and Disease Characteristics from Phase 2b/3 trial (VTS301) Part A/B

	Adrabetadex (N=36)	Sham Control (N=19)
Age (years), mean (SD)	12.7 (5.64)	11.7 (5.10)
Male, n (%)	22 (58)	8 (44)
Weight (kg), mean (SD)	48.1 (25.27)	40.2 (18.98)
Miglustat use,* n (%)	25 (66)	9 (50)
Seizures, n (%)	15 (39)	5 (28)
Duration of neurologic symptoms (years), mean (SD)	7.1 (4.15)	5.9 (5.16)
Baseline NPC-CSS total score (minus hearing/ABR), mean (SD)	17.8 (6.48)	16.9 (8.16)

*Participants with record of miglustat use prior to receiving the first dose of study drug.

Abbreviations: ABR=auditory brain response; NPC-CSS=Niemann-Pick type C Clinical Severity Scale; SD=standard deviation.

Safety

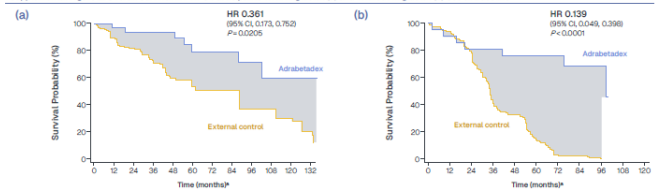
- Adverse events with ≥30% higher incidence in the adrabetadex–treated vs sham group included vomiting, hypoacusis, back pain, diarrhea, gait disturbance, and fatigue; treatment-related events with ≥30% higher incidence were vomiting, hypoacusis, back pain, and fatigue (**Supplemental Table 3**).
- No participants discontinued the study due to treatment-emergent adverse events (TEAEs) in Part A/B of VTS301.

Supplemental Table 3. Summary of Safety (Phase 2b/3 trial [VTS301] Part A/B, Safety Population)

	Adrabetadex (n=36)	Sham Control (n=18)
Any TEAE, n (%)	36 (100)	17 (94)
Non-fatal treatment-emergent SAE, n (%)	20 (53)	4 (22)
SAE occurring in >1 participant receiving adrabetadex, n (%)		
Hearing impaired	4 (11)	1 (6)
Pneumonia, aspiration	4 (11)	1 (6)
Deafness	3 (8)	0 (0)
Seizure	3 (8)	1 (6)
Dysphagia	2 (5)	1 (6)
Aspiration	2 (5)	1 (6)

Abbreviations: SAE=serious adverse event; TEAE=treatment-emergent adverse event.

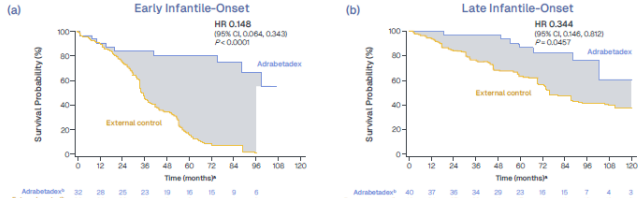
Supplemental Figure 2. Overall Survival in I-NPC Participants With Miglustat (a) and Without Miglustat (b) Use at Baseline



*KM curves are visually truncated at ~132 months in panel a and ~96 months in panel b. †Weighted numbers at risk are shown for external control individuals to account for the many-to-1 matching to treated patients.

Abbreviations: I-NPC=infantile-onset Niemann-Pick disease type C; HR=hazard ratio; KM=Kaplan-Meier; OS=overall survival.

Supplemental Figure 3. Overall Survival in Participants With Early (a) and Late (b) I-NPC



*KM curves are visually truncated at ~120 months. †Weighted numbers at risk are shown for external control individuals to account for the many-to-1 matching to treated patients.

Abbreviations: I-NPC=infantile-onset Niemann-Pick disease type C; HR=hazard ratio; KM=Kaplan-Meier; OS=overall survival.

References

1. Beren Therapeutics P.B.C. Data on file.

Acknowledgements

This study was funded by Beren Therapeutics P.B.C. Medical writing support was provided by Ana Mata, PhD, Carolyn M. Walsh, PhD, and Tiago Silva, PharmD, PhD, CMPP, of Med Communications, Inc, with funding from Beren Therapeutics P.B.C.

We thank the patients, caregivers, adrabetadex EAP, and VTS301 investigators involved in this program.

Presented at the NORD Breakthrough Summit | October 25-27, 2026 | Washington, DC | USA

Survival outcomes by baseline disease burden in participants with infantile-onset Niemann-Pick disease type C treated with adrabetadex

Poster 26

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BACKGROUND

- Niemann–Pick disease type C (NPC) is a lethal, rare, progressive, neurodegenerative genetic disorder caused by impaired cholesterol trafficking, resulting in cholesterol accumulation and downstream cellular dysfunction.[1,2]
- Disease severity and progression are strongly influenced by age of neurological onset, with infantile-onset (I-NPC; neurological onset <6 years of age) representing the most severe phenotype.[1,2]
- Mean age of death has been reported as 5.6 years in early I-NPC (neurological onset <2 years of age) and 13.4 years in late I-NPC (2 to <6 years of age), consistent with more rapid disease progression in earlier-onset disease.[3]
- Adrabetadex is an investigational intrathecal therapy for I-NPC and the only therapy designed to directly target accumulated intracellular cholesterol in the CNS, the central pathogenic driver of NPC, by restoring cholesterol trafficking.
- Adrabetadex is the only therapy studied in I-NPC and shown to improve survival in both early and late I-NPC (overall survival in I-NPC compared with matched external controls, HR [95% CI]: 0.289 [0.141, 0.593]; p<0.0001).[4]
- Because cholesterol accumulation drives progressive neuronal cell loss and neurodegeneration,[5,6] baseline disease burden at treatment initiation may influence long-term survival outcomes. Earlier removal of accumulated cholesterol and restoration of cholesterol trafficking may reduce the rate of neurological decline and improve long-term survival.
- This analysis evaluated overall survival in adrabetadex-treated participants with I-NPC stratified by baseline disease burden using a rescored 4-domain NPC Clinical Severity Scale (R4DNPCCSS; ambulation, fine motor skills, speech, rescored swallowing).

OBJECTIVES

To evaluate overall survival among individuals with I-NPC treated with adrabetadex, stratified by baseline disease burden as assessed using a rescored 4-domain NPC Clinical Severity Scale.

METHODS

Disease Burden Stratification

- Individuals with I-NPC (neurological onset <6 years) treated with adrabetadex in clinical studies or the Expanded Access Program were included.
- Baseline R4DNPCCSS scores (0–20 composite score; higher scores indicate greater impairment) were used to stratify participants into disease burden groups defined by tertiles: low (≤4), medium (5 to 9), high (10 and above).
  - The R4DNPCCSS is a modified version of the 5 domain NPCCSS, which includes the domains most relevant to patients, caregivers, and clinicians: ambulation, swallowing, cognition, speech, and fine-motor.[7]
  - The R4DNPCCSS eliminates the cognitive domain and adds an improved swallow scoring algorithm.[7]

Overall Survival

- Overall survival was estimated using Kaplan–Meier (KM) method.
- Estimates of survival across score tertiles at baseline were compared using a log-rank test for trend.

RESULTS

Baseline characteristics (Table 1)

- Seventy-six treated participants were included in the analysis stratified by low (n=29, 38.2%), medium (n=23, 30.3%), and high (n=24, 31.6%) baseline R4DNPCCSS scores.
- The age at neurological symptom onset and the distribution of early and late infantile-onset participants are generally comparable across tertiles.
- The low tertile has a lower median age at start of adrabetadex treatment than the medium and high tertiles.
- There are no apparent differences in baseline miglustat use between tertiles.

Table 1. Baseline Demographics and Disease Characteristics

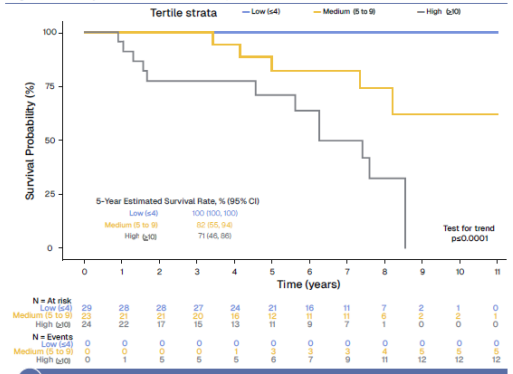
Baseline Characteristics	Low Tertile (R4DNPCCSS ≤4) (n=29)	Medium Tertile (R4DNPCCSS 5 to 9) (n=23)	High Tertile (R4DNPCCSS 10 and above) (n=24)	Overall (n=76)
Age at symptom onset category, n (%)				
<2 years old	11 (37.9)	11 (47.8)	11 (45.8)	33 (43.4)
2–6 years old	18 (62.1)	12 (52.2)	13 (54.2)	43 (56.6)
Age at neurological symptom onset, years	n=29	n=23	n=24	n=76
Mean (SD)	2.5 (1.54)	2.5 (1.71)	2.5 (1.51)	2.5 (1.56)
Median (Q1, Q3)	2.1 (1.1, 4.0)	2.0 (1.2, 4.0)	2.1 (1.3, 3.7)	2.0 (1.1, 4.0)
Age at adrabetadex treatment start, years				
Mean (SD)	5.7 (4.55)	9.0 (5.95)	8.7 (5.79)	7.7 (5.56)
Median (Q1, Q3)	4.7 (3.0, 6.6)	8.8 (4.5, 12.7)	8.6 (3.4, 11.3)	6.2 (3.2, 10.8)
Sex, n (%)				
Male	20 (69.0)	11 (47.8)	10 (41.7)	41 (53.9)
Female	9 (31.0)	12 (52.2)	14 (58.3)	35 (46.1)
Race				
Asian	0	2 (8.7)	1 (4.2)	3 (3.9)
White	28 (96.6)	21 (91.3)	17 (70.8)	66 (86.8)
Multiple	0	0	1 (4.2)	1 (1.3)
Other	0	0	5 (20.8)	5 (6.6)
Not Reported	1 (3.4)	0	0	1 (1.3)
Miglustat use at baseline[a]				
Yes	15 (51.7)	15 (65.2)	11 (45.8)	41 (53.9)
No	14 (48.3)	8 (34.8)	13 (54.2)	35 (46.1)
R4DNPCCSS baseline value[b]				
Mean (SD)	2.3 (1.28)	6.8 (1.35)	13.4 (3.12)	7.2 (5.06)
Median (Q1, Q3)	2.0 (1.0, 3.0)	7.0 (5.0, 8.0)	12.0 (10.5, 16.0)	7.0 (3.0, 10.0)

Percentages are based on the total number of patients (n).
Q1, first quartile; Q3, third quartile; R4DNPCCSS, Composite Outcome (Ambulation, Speech, Fine Motor, Rescored Swallowing); SD, standard deviation.
[a]Miglustat use at baseline is derived from concomitant medications. Miglustat use was derived as Yes if there was a record of miglustat use in the concomitant medications at or prior to the first dose of study medication. Otherwise, miglustat use is No.
[b]Four patients out of 80 were missing baseline R4DNPCCSS scores. They are excluded from the analysis. Max, maximum; Min, minimum; Q1, first quartile; Q3, third quartile; R4DNPCCSS, rescored 4-domain Niemann–Pick disease type C clinical severity scale; SD, standard deviation.

Survival

- Participants received adrabetadex treatment for up to 11.325 years. At 5 years, KM–estimated overall survival was 100% (95% CI: 100%, 100%) in the low R4DNPCCSS group, 82% (95% CI: 55%, 94%) in the medium group, and 71% (95% CI: 46%, 86%) in the high group (Figure 1).

Figure 1. Survival by Baseline R4DNPCCSS Score (tertile)



CONCLUSIONS

- Adrabetadex-treated participants with the lowest baseline disease burden (R4DNPCCSS ≤4) demonstrated the longest observed survival, including 100% survival at 5 years in the lowest severity group, consistent with earlier intervention before irreversible neurodegeneration.
- Five-year survival exceeded 70% across all disease burden tertiles and was numerically higher than previously reported survival in matched external control populations (42%).[4]
- Findings are consistent with the hypothesis that earlier restoration of cholesterol trafficking may improve long-term outcomes when initiated before advanced neurodegeneration.
- Given the rapid progression, high unmet need, and limited treatment options in the youngest patients with I-NPC, these findings support the importance of early diagnosis and prompt initiation of adrabetadex as foundational therapy.

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1. Vanier MT. *Orphanet J Rare Dis.* 2010;5:16. 2. Imrie J, et al. *BMC Neurol.* 2015;15:257. 3. Bianconi S, et al. *Mol Genet Metab Rep.* 2019;126:466–469. 4. Berry-Kravis E, et al. *Mol Genet Metab.* 2026;147:109341. 5. Reid PC, et al. *J Lipid Res.* 2004;45:582–591. 6. Aqul A, et al. *J Neurosci.* 2011;31(25):9404–9413. 7. Mengel E, et al. Mol Genet Metab Rep. 2025;43:101233.

Acknowledgments

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Early evidence of an emerging NPC treatment paradigm: adrabetadex use alongside arimoclomol and/or N-acetyl-L-leucine

Poster 6

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BACKGROUND

- Niemann-Pick disease type C (NPC) is a rare, progressive, neurodegenerative disorder caused by impaired cholesterol trafficking, resulting in cholesterol accumulation and downstream cellular dysfunction.[1]
- FDA-approved therapies for the neurological manifestations of NPC have distinct mechanisms of action, including arimoclomol (heat shock protein co-induction; approved in combination with miglustat (substrate reduction), for patients ≥2 years of age), and N-acetyl-L-leucine (NALL; modified amino acid therapy approved for patients with NPC weighing ≥15 kg).[2-4]
- Adrabetadex is an investigational intrathecal therapy for infantile-onset (I-NPC) and the only therapy designed to directly target accumulated intracellular cholesterol in the CNS, the central pathogenic driver of NPC, by restoring cholesterol trafficking.
- Adrabetadex remains the only therapy studied and shown to improve survival in both early and late I-NPC compared with matched external controls.[5]
- Because adrabetadex targets the central pathogenic driver of disease, complementary therapies with distinct mechanisms may be layered on top to address downstream manifestations or provide additive benefit.
- In a recent consensus publication, most experts completely or partially agreed that combination therapy should be considered for patients with confirmed NPC; however, limited data are available regarding initiation and use of combination therapy outside of miglustat.[4]
- This analysis represents the first systematic evaluation of treatment sequencing and combination therapy in NPC, characterizing the use of adrabetadex alongside arimoclomol and/or NALL in clinical practice.

OBJECTIVES

To describe baseline characteristics, treatment sequencing, and combination therapy patterns in a cohort of participants treated with adrabetadex plus arimoclomol and/or NALL in an adrabetadex expanded access program (EAP), and to explore evidence for an emerging

RESULTS

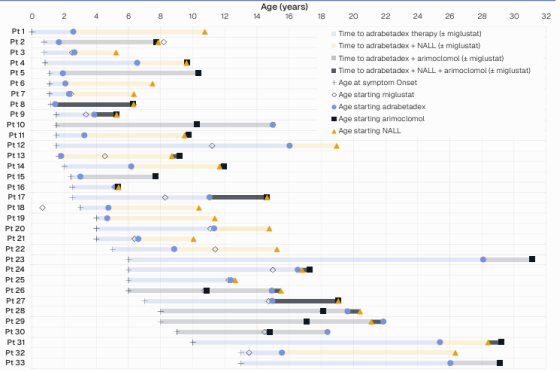
- At the data cutoff of March 1, 2026, 33 participants had received adrabetadex with arimoclomol and/or NALL: 6 participants received adrabetadex with arimoclomol, 12 received adrabetadex with NALL, and 15 received adrabetadex, arimoclomol, and NALL (Table 1).
- All 33 participants received adrabetadex, while 27 (81.8%) received NALL, 21 (63.6%) arimoclomol, and 20 (60.6%) miglustat; 10 participants were exposed to all four therapies.
- Of these, 28 participants received adrabetadex through the EAP and then began treatment with arimoclomol and/or NALL following U.S. approval.
- A total of 5 participants (juvenile onset, n=3; late I-NPC, n=1; early I-NPC, n=1) received arimoclomol before U.S. approval and later added treatment with adrabetadex, following the approval of arimoclomol. These participants received arimoclomol for an average of 3.71 years before initiating treatment with adrabetadex.

Table 1. Baseline Demographics and Disease Characteristics

	Adrabetadex + Arimoclomol (n=6)	Adrabetadex + NALL (n=12)	Adrabetadex + Arimoclomol + NALL (n=15)	ISS EAP Pool (N=85)
Age at neurological symptom onset category, n (%)				
<2 years old	2 (33.3)	5 (41.7)	6 (40.0)	26 (30.6)
2–6 years old	1 (16.7)	5 (41.7)	3 (20.0)	27 (31.8)
≥6 years old	3 (50.0)	2 (16.7)	6 (40.0)	31 (36.5)
Missing	0	0	0	1 (1.2)
Age at neurological symptom onset, years	n=6	n=12	n=15	N=84
Mean (SD)	5.5 (4.77)	3.6 (3.50)	4.0 (3.16)	5.8 (6.12)
Median (Q1, Q3)	4.2 (1.5, 9.0)	3.5 (1.1, 4.5)	2.5 (1.5, 7.0)	4.0 (1.5, 7.0)
Age at adrabetadex treatment start, years	n=6	n=12	n=15	N=84
Mean (SD)	15.2 (11.32)	6.8 (4.86)	9.8 (8.25)	11.8 (10.20)
Median (Q1, Q3)	16.7 (3.0, 26.0)	5.0 (2.0, 11.5)	6.0 (3.0, 16.0)	8.0 (3.0, 20.5)
Sex, n (%)				
Male	4 (66.7)	6 (50.0)	8 (53.3)	52 (61.2)
Female	2 (33.3)	6 (50.0)	7 (46.7)	32 (37.6)
Unknown	0	0	0	1 (1.2)
Race, n (%)				
Black or African American	0	0	0	1 (1.2)
White	6 (100.0)	11 (91.7)	14 (93.3)	74 (87.1)
Other	0	0	1 (6.7)	5 (5.9)
Multiple	0	1 (8.3)	0	1 (1.2)
Not Reported	0	0	0	4 (4.7)
Miglustat use at Baseline,[a] n				

Early evidence of an emerging NPC treatment paradigm:

Figure 1. Timeline of Adrabetadex, Miglustat, Arimoclomol, and NALL Therapy for Individual Participants



- Of the 20 miglustat-treated participants, 15 had initiated miglustat prior to adrabetadex.
- Fifteen participants received adrabetadex, arimoclomol, and NALL. Of these, 12 participants initiated therapy with adrabetadex first and 3 initiated arimoclomol first. The sequence of therapy additions to adrabetadex in these 12 participants varied: 5 added arimoclomol and NALL simultaneously, 4 added NALL followed by arimoclomol, and 3 added arimoclomol followed by NALL.

Hydroxypropyl-β-cyclodextrine (HPβCD) IT

- **2017 – Phase I/II**
- Premiers résultats encourageants sur le ralentissement de la progression neurologique.
- **2021 – Phase IIb/III**
- Absence de supériorité sur le groupe contrôle. Arrêt du programme de développement initial.
- **2025 – Reprise du développement**
- Recentrage sur les formes infantiles. Obtention du statut Breakthrough Therapy auprès de la FDA.
- **2026 – Nouvelles données cliniques**
- Ralentissement de la progression neurologique de 43 % (données du laboratoire).
- Réduction du risque de décès de 55 % (analyse de la FDA).
- 17 novembre 2026 – Autorisation FDA
- Lembaz® pour les formes à début neurologique avant l'âge de 6 ans, chez les patients de 7 kg et plus.



Research Paper

Low Risk Profile of Long-Term Repeated Lumbar Puncture for Intrathecal Delivery of 2-Hydroxypropyl-Beta-Cyclodextrin in Patients With Niemann-Pick Type C

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Adrabetadex
Cyclodextrin
Intrathecal infusion
Niemann-Pick type C

ABSTRACT

Background: Intrathecal delivery of 2-hydroxypropyl-beta-cyclodextrin (VTS-270, adrabetadex) by lumbar puncture (LP) has been performed on a biweekly schedule for over nine years for the treatment of Niemann-Pick type C1 (NPC1) at Rush University Medical Center.
Methods: Over this time 59 patients with NPC1 have been treated with 2935 infusions, performed with either a 22-G 3-inch Whitacre or a 22-G 2-inch Gertie Marx atraumatic needles, with or without general anesthesia. Adverse events potentially related to the LP infusion were collected from records for all patients treated for NPC. The NPC1 cohort ranged in age from one to 31 years at the initiation of treatment.
Results: Of the 59 patients treated 33 (55.9%) had no adverse events ever after an LP and 26 (44.1%) had adverse effects at some time. Of the 2935 LPs, adverse events occurred after 3.3% of LPs. Adverse events most observed were headache (1.2% of LPs), nausea (0.3%), vomiting (1.0%), and back pain (1.3%).
Conclusions: This study shows that frequent repeated LPs are possible for delivery of intrathecal therapy and can be accomplished with a very low rate of post-LP adverse events.
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FDA NEWS RELEASE

FDA Approves First Drug Shown to Help Patients with Infantile-Onset Niemann-Pick Disease Type C Live Longer

New therapy offers a meaningful treatment option for families facing a rare and serious childhood disease

For Immediate Release: November 17, 2026

The U.S. Food and Drug Administration today approved Lembaz (adrabetadex) injection, the first treatment shown to help people with a severe form of Niemann-Pick disease type C (NPC) live longer. Lembaz is approved to reduce the risk of death in adult and pediatric patients who weigh at least 7 kg (about 15 pounds) and whose neurological symptoms began before age 6, also known as infantile-onset NPC.

Transplantations


Vanier Orphanet Journal of Rare Diseases 2010, 5:16
http://www.ojrd.com/content/5/1/16

ORPHANET JOURNAL OF RARE DISEASES

REVIEW Open Access

Niemann-Pick disease type C

Marie T Vanier[1,2]

1. Greffe de cellules souches hématopoïétiques (CSH)

- **NPC1 :** absence de bénéfice neurologique dans les modèles murins et chez les rares patients greffés.
- Amélioration possible des manifestations viscérales, notamment de l'hépatosplénomégalie, sans effet sur la neurodégénérescence.

2. Transplantation hépatique

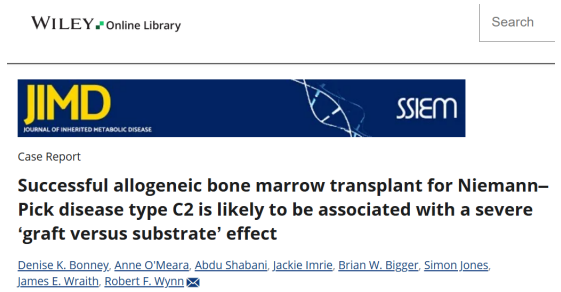
- Réalisée chez quelques patients NPC1 présentant une atteinte hépatique sévère (cirrhose).
- **Aucun bénéfice démontré sur l'évolution neurologique.**

3. Cas particulier de la maladie NPC2

- Quelques greffes précoces de CSH rapportées.
- Résultats encourageants dans certains cas, mais recul insuffisant pour évaluer

le bénéfice neurologique à long terme.

- Bonney et al. (2010) : cas d'un enfant greffé précocement, vivant à l'âge de 3 ans.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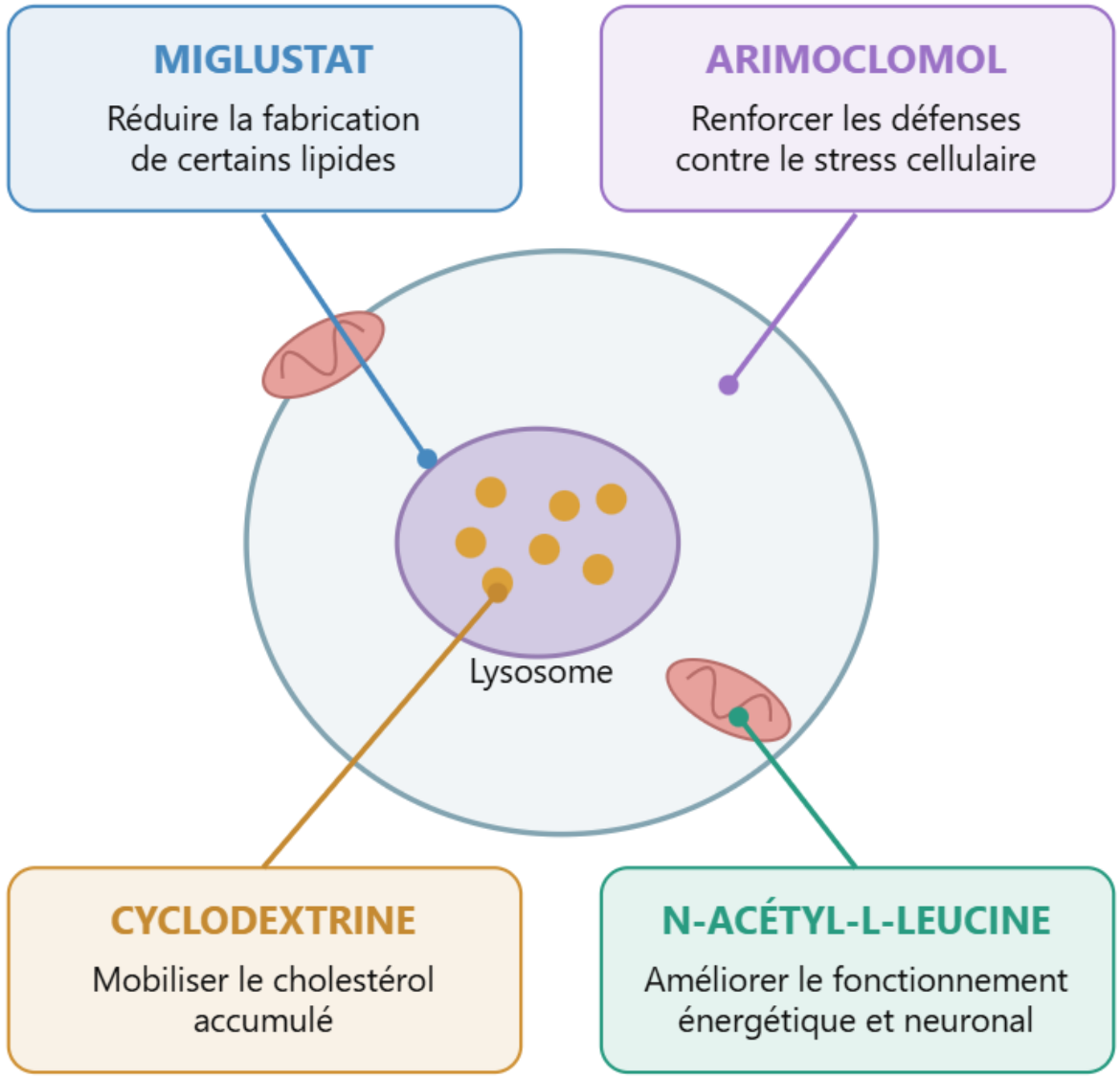
Case Report

Successful allogeneic bone marrow transplant for Niemann–Pick disease type C2 is likely to be associated with a severe 'graft versus substrate' effect

Denise K. Bonney, Anne O'Meara, Abdu Shabani, Jackie Imrie, Brian W. Bigger, Simon Jones, James E. Wraith, Robert F. Wynn

Quatre traitements, quatre approches complémentaires



Nouvelles stratégies thérapeutiques (modèles animaux)

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REVIEW ARTICLE

Treatment trials in Niemann-Pick type C disease

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1. Hydroxypropyl-β-cyclodextrine (HPβCD) — Mobilisation du cholestérol

- Favorise la sortie du cholestérol accumulé dans les lysosomes, indépendamment de NPC1/NPC2.
- Réduction de la surcharge lipidique et de la neurodégénérescence chez l'animal.
- Limites : faible passage de la barrière hémato-encéphalique par voie systémique et toxicités potentielles.

2. Vorinostat — Modulation épigénétique

- Inhibiteur des histones désacétylases (HDAC).
- Amélioration de l'atteinte hépatique chez la souris.
- Efficacité neurologique limitée par son faible passage cérébral.

3. Associations de traitements : des résultats précliniques encourageants

- **Miglustat + ibuprofène :** prolongation de la survie supérieure à celle obtenue avec chaque molécule seule.
- **Miglustat + curcumine :** augmentation de la survie d'environ 84 % chez la souris NPC1 (Williams et al., 2014).
- **Vorinostat + HPβCD + PEG (polyéthylène glycol,** composant de formulation destiné à améliorer la délivrance du traitement)**:** meilleure pénétration cérébrale du vorinostat, préservation des cellules de Purkinje et prolongation de la survie dans un modèle murin.

4. Thérapie génique : restaurer la fonction NPC1

- Expression ciblée de NPC1 dans les neurones ou les cellules gliales.
- Correction partielle de l'accumulation cérébrale de cholestérol.
- Préservation des cellules de Purkinje lorsque NPC1 est réexprimée dans ces neurones.
- Résultats prometteurs, mais encore expérimentaux dans cette revue.

A venir ?

biomedicines

MDPI

Systematic Review

Therapeutic Interventions in Niemann–Pick Disease Type C: A Systematic Review of Clinical Outcomes and Safety

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5.	Phase 1/2 Study of Vorinostat Therapy in Niemann–Pick Disease, Type C1 [28] Study design: Phase I/II, open-label, single-group trial; NCT02124083	**Intervention:** Vorinostat (n = 12) **Comparator**: None	**Age**: 18–65 years; **Sex**: 6 male/6 female	Completion of the 200 mg and 400 mg treatment phases at three months	All 12 completed the 200 mg phase and 11/12 completed the 400 mg phase. Cathepsin D was 648.2 ± 266.0 ng/mL at baseline and 625.3 ± 183.8 at six months. Galectin-3 was 6.667 ± 2.303 and 6.565 ± 4.775 ng/mL, respectively.	Serious AEs occurred in 5/12 (41.7%); non-serious AEs in 11/12 (91.7%). Serious events included vomiting, Epstein–Barr viremia, fever, cerebrospinal fluid leakage, abnormal liver tests, and aspiration pneumonia. No deaths occurred.

S.NO	STUDY TITLE & DESIGN	INTERVENTIONS & COMPARATOR	POPULATION DEMOGRAPHICS	PRIMARY OUTCOMES	RESULTS	ADVERSE EVENTS (AE)
1.	Efficacy and safety of efavirenz in Niemann–Pick disease type C [22] **Study design:** Phase II, single-center, single-arm, open-label trial	**Intervention:** Efavirenz (n = 16) **Comparator**: None	**Age**: 15–60 years **Sex**: 11 males/5 females	Proportion of responders at Week 52, defined as no deterioration in ≥2 of 3 cognitive domains: CDR-SB, Free and Cued Selective Reminding Test (FCSRT), and executive-function tests	All 16 participants responded at Week 52 (100%; 95% CI 79.4–100.0%); 15/16 responded earlier. This represented non-deterioration in ≥2 domains, not universal improvement. Post hoc favorable-response and unfavorable-response groups differed mainly by disease duration. SARA and PDS were broadly stable; EAT-10 and WAIS-III improved. Cerebrospinal fluid amyloid-beta increased and tau remained stable.	Three AEs occurred in one participant: traumatic brain injury, splenic laceration following an ataxia-related fall, and myelocytic leukemia. All were considered unrelated to efavirenz; no treatment-related serious AEs occurred.

Table 6. Studies retrieved from the databases for nizubaglustat.

S.NO.	STUDY TITLE & DESIGN	INTERVENTIONS & COMPARATOR	POPULATION DEMOGRAPHICS	PRIMARY OUTCOMES	RESULTS	ADVERSE EVENTS (AE)
1.	The RAINBOW study: a phase 2 trial evaluating the 3-month pharmacokinetic and pharmacodynamic data and 18-month clinical and safety outcomes of nizubaglustat in GM2 gangliosidoses or Niemann–Pick type C disease [23] **Study design:** Phase II, multicenter trial with a 12-week randomized, double-blind, placebo-controlled phase and optional active-treatment extension	**Intervention:** Nizubaglustat 3 mg/day (n = 5) or 9 mg/day (n = 4) **Comparator:** Placebo (n = 4)	**Age**: 12–38 years **Sex**: 7 male/6 female	Pharmacokinetics (PK); pharmacodynamics (PD) of C16/C18 ceramides and glucosylceramides; 12-week safety	Absorption peaked at 2–6 h. The 9 mg dose produced higher exposure and reduced C16 and C18 glucosylceramides by up to 87% and 47%, respectively; ceramides were unchanged. At 15–18 months, 4/11 improved, 1 remained stable, and 6 worsened on SARA; 6/11 improved on either SARA or INAS.	At Week 12, 10/13 experienced only mild or moderate treatment-emergent AEs. 44 long-term events, skin events occurred in 7/13. One unrelated serious liver abscess occurred. No deaths or AE-related discontinuations occurred.

1. Vorinostat : piste thérapeutique expérimentale

- Médicament développé pour traitement de certains cancers
- Avec pour objectif dans maladie de NPC de restaurer partiellement le fonctionnement de la protéine NPC1 : amélioration du repliement, de la stabilité et du traffic intracellulaure de certaines protéines NPC1 mutées
- Essai clinique en 2018 phase 1/2: 12 patients, absence de bénéfice démontré et EI graves chez plus de 40% des patients

2. Nizubaglustat

- Médicament per os, proche du miglustat, avec inhibition de la glucosylcéramide synthase (GCS) et de la glucosylcéramidase non lysosomale (GBA2)
- Passe la BHE
- Étude de phase 2 publiée en 2026
- 13 patients: 7 patients GM2 et 6 NPC, 3 groupes de traitements (3mg/jour, 9mg/jour ou placebo) pendant 12 semaines
- 15-18m de traitements : 4 patients NPC (2 sortis études pour accès miglustat): 45.5% ont une amélioration du score SARA, 54% du SARA fonctionnel, 63% du score INAS (non ataxia signs)
- Profil tolérance initial favorable, absorption rapide

3. Efavirenz

- Traitement initialement développé comme anti rétroviral (VIH)
- Active la choelstérol hydroxylase (CYP46A1), enzyme exprimée dans les neurones et qui transforme le cholestérol en 24SOHclt capable de traverser la BHE : objectif de favoriser le renouvellement et l'élimination du cholestérol cérébral
- Étude de phase 2, en ouvert, publiée en 2025, en plus du traitement habituel
- 16 patients avec forme juvénile tardive ou adulte et atteinte cognitive
- Voie orale 25mg/J jusque 26ième sem -> 100% absence dégradation 2/3 critères (démense, mémoire verbale et fonctions exécutives) puis 100mg/j jusqu'à 52ième sem
- 3 EI

Take home messages

JOURNÉE NATIONALE
PATIENTS & FAMILLES
Niemann-Pick C



- Des traitements qui ciblent différents mécanismes de la maladie.
- La perspective d'associer plusieurs approches thérapeutiques.
- De nouvelles molécules et stratégies encore en développement.
- Des avancées thérapeutiques considérables en moins de 20 ans.
- Un enjeu majeur : **permettre aux patients français d'accéder aux innovations thérapeutiques**