1er CONGRÈS FRANCOPHONE MULTIDISCIPLINAIRE DE L'AMYLOSE
2012-2022: retour sur 10 années d'innovations
Vendredi 17 juin 2022
Espace Saint-Martin ■ PARIS
www.congres-amylose.com

Le traitement des neuropathies héréditaires à transthyrétine en 2022 (et après)

Pr Andoni ECHANIZ-LAGUNA

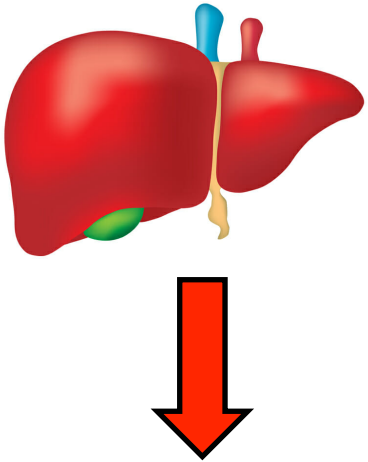
Centre de Référence
Neuropathies Rares
CHU Bicêtre

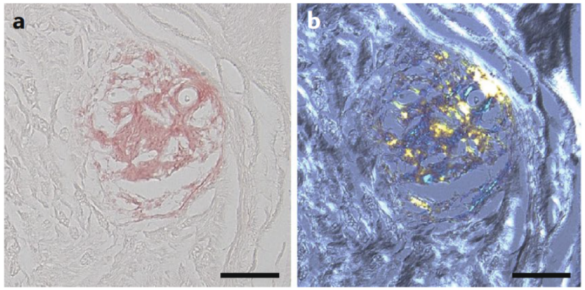
L’amylose héréditaire à transthyrétine

- autosomique dominant
- mutations gène transthyrétine -TTR
- TTR sécrétée par le foie
- mutations ponctuelles
  - protéine TTR malformée
  - accumulation protéine TTR toxique
- gain de fonction toxique

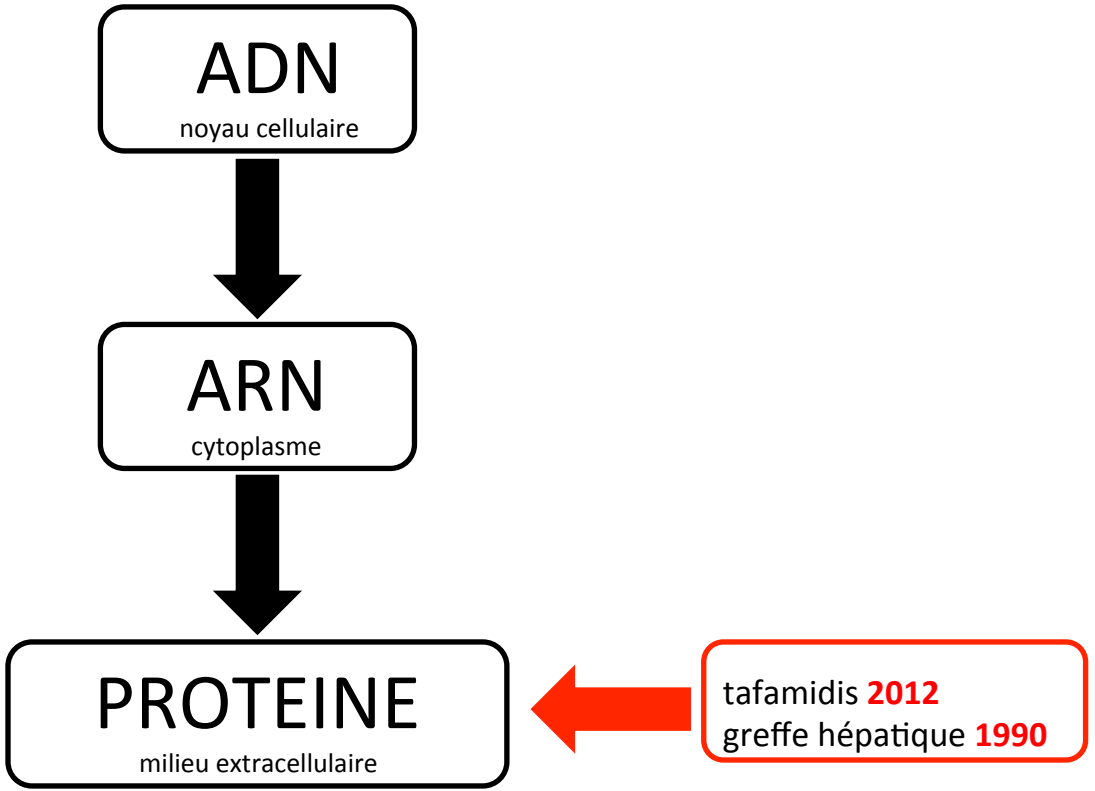
- les souris KO TTR sont normales

▸ on peut vivre sans le gène TTR!

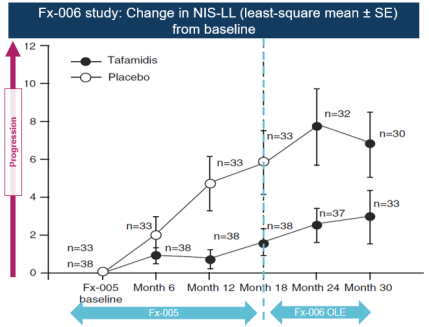


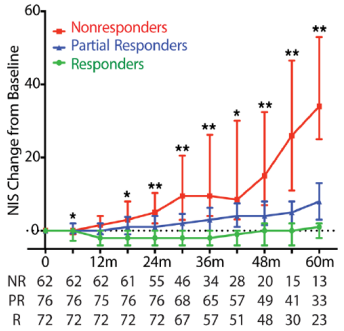


l'amylose héréditaire à transthyrétine



Tafamidis (NIS)





- Population étudiée: V30M early
- Résultats à 30 mois
- Paramètre étudiée = NIS LL
- **NIS à l'inclusion = 6**

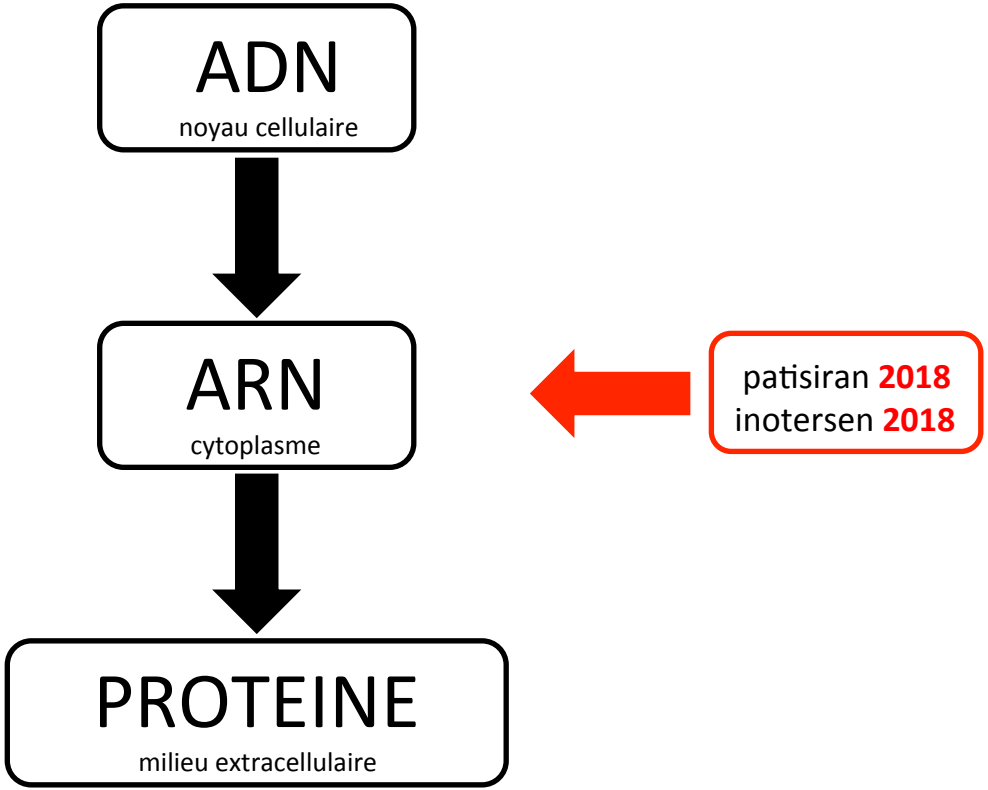
Progression *VS* Baseline moins rapide que PBO

Sur 210 patients V30M early[1] :

- 34% répondeurs
- 36 % répondeurs partiels

- 30% non- répondeurs (**NIS>10**)

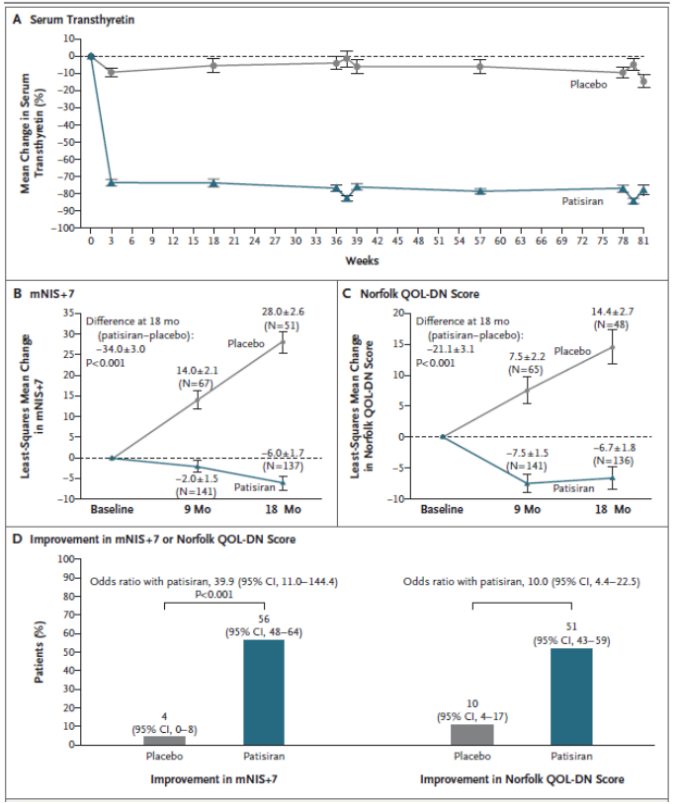
l'amylose héréditaire à transthyrétine



Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis

D. Adams, A. Gonzalez-Duarte, W.D. O'Riordan, C.-C. Yang, M. Ueda, A.V. Kristen, I. Tournev, H.H. Schmidt, T. Coelho, J.L. Berk, K.-P. Lin, G. Vita, S. Attarian, V. Planté-Bordeneuve, M.M. Mezei, J.M. Campistol, J. Buades, T.H. Brannagan III, B.J. Kim, J. Oh, Y. Parman, Y. Sekijima, P.N. Hawkins, S.D. Solomon, M. Polydefkis, P.J. Dyck, P.J. Gandhi, S. Goyal, J. Chen, A.L. Strahs, S.V. Nochur, M.T. Sweetser, P.P. Garg, A.K. Vaishnaw, J.A. Gollob, and O.B. Suhr

New Engl J Med, 2018



Long-term safety and efficacy of patisiran for hereditary transthyretin-mediated amyloidosis with polyneuropathy: 12-month results of an open-label extension study

*David Adams, Michael Polydefkis, Alejandra González-Duarte, Jonas Wixner, Arnt V Kristen, Hartmut H Schmidt, John L Berk, Inés Asunción Losada López, Angela Dispenzieri, Dianna Quan, Isabel M Conceição, Michel S Slama, Julian D Gillmore, Theodoros Kyriakides, Senda Ajroud-Driss, Márcia Waddington-Cruz, Michelle M Mezei, Violaine Planté-Bordeneuve, Shahram Attarian, Elizabeth Mauricio, Thomas H Brannagan III, Mitsuharu Ueda, Emre Aldinc, Jing Jing Wang, Matthew T White, John Vest, Erhan Berber, Marianne T Sweetser, Teresa Coelho, on behalf of the patisiran Global OLE study group**

Lancet Neurol, 2021

Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis

M.D. Benson, M. Waddington-Cruz, J.L. Berk, M. Polydefkis, P.J. Dyck, A.K. Wang, V. Planté-Bordeneuve, F.A. Barroso, G. Merlini, L. Obici, M. Scheinberg, T.H. Brannagan III, W.J. Litchy, C. Whelan, B.M. Drachman, D. Adams, S.B. Heitner, I. Conceição, H.H. Schmidt, G. Vita, J.M. Campistol, J. Gamez, P.D. Gorevic, E. Gane, A.M. Shah, S.D. Solomon, B.P. Monia, S.G. Hughes, T.J. Kwoh, B.W. McEvoy, S.W. Jung, B.F. Baker, E.J. Ackermann, M.A. Gertz, and T. Coelho

New Engl J Med, 2018

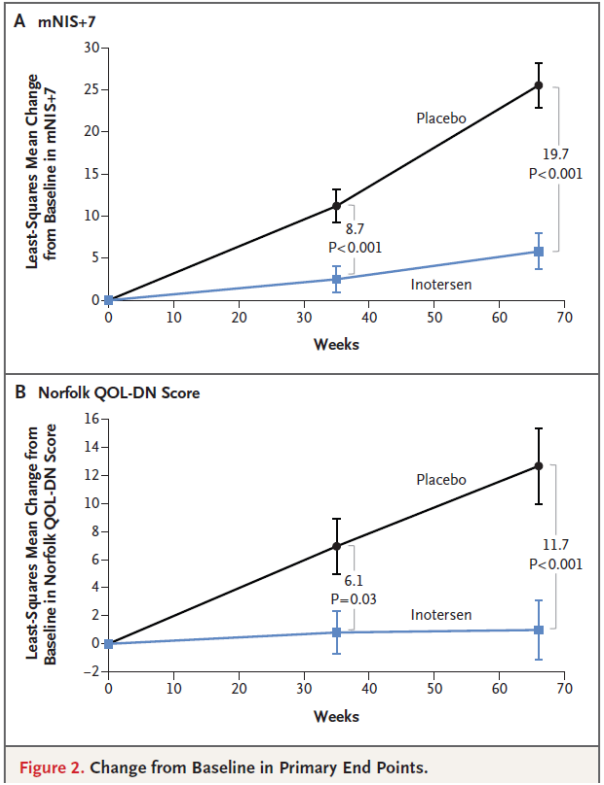
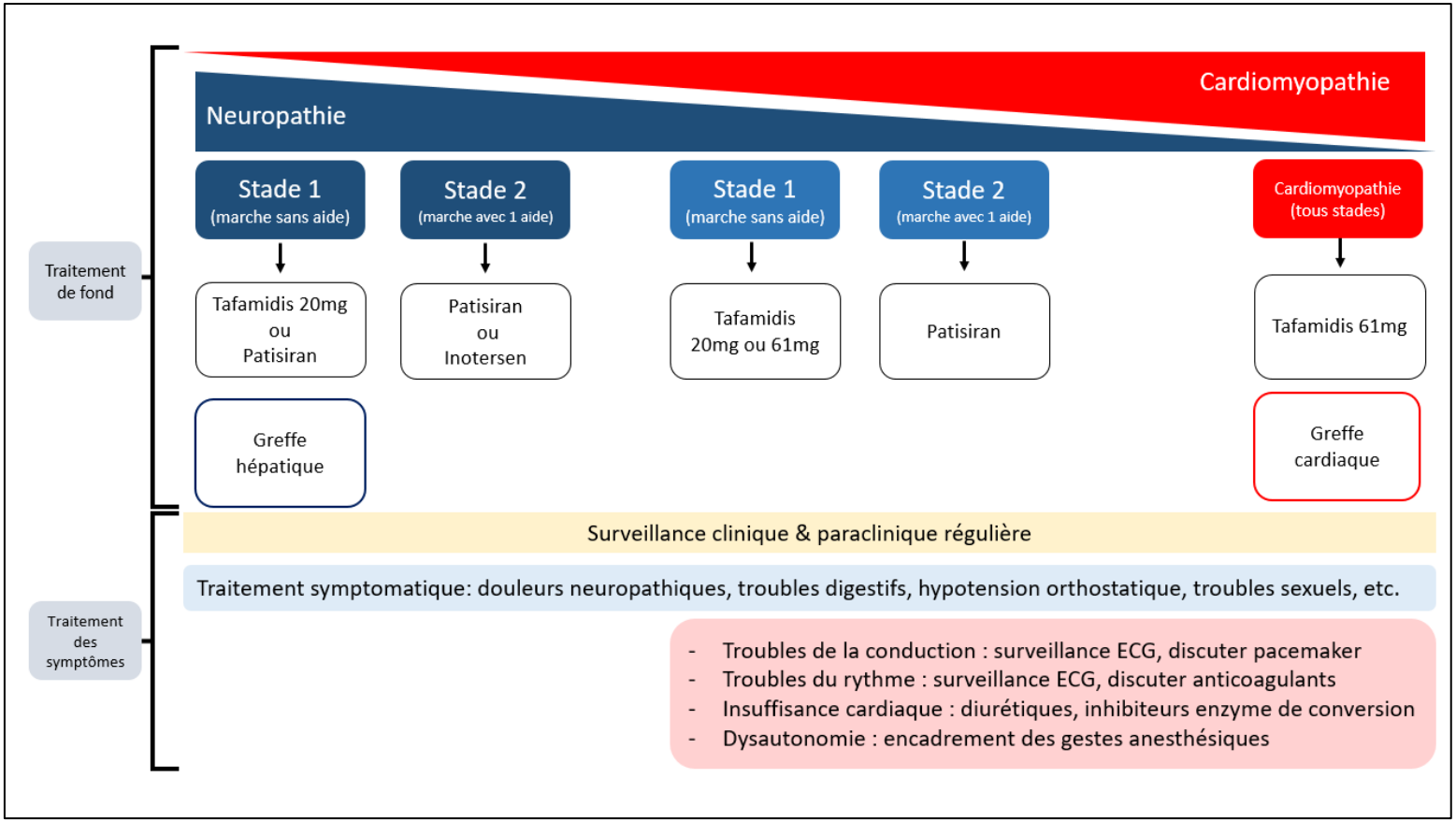
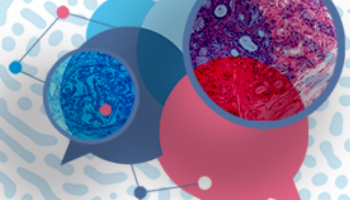


Figure 2. Change from Baseline in Primary End Points.

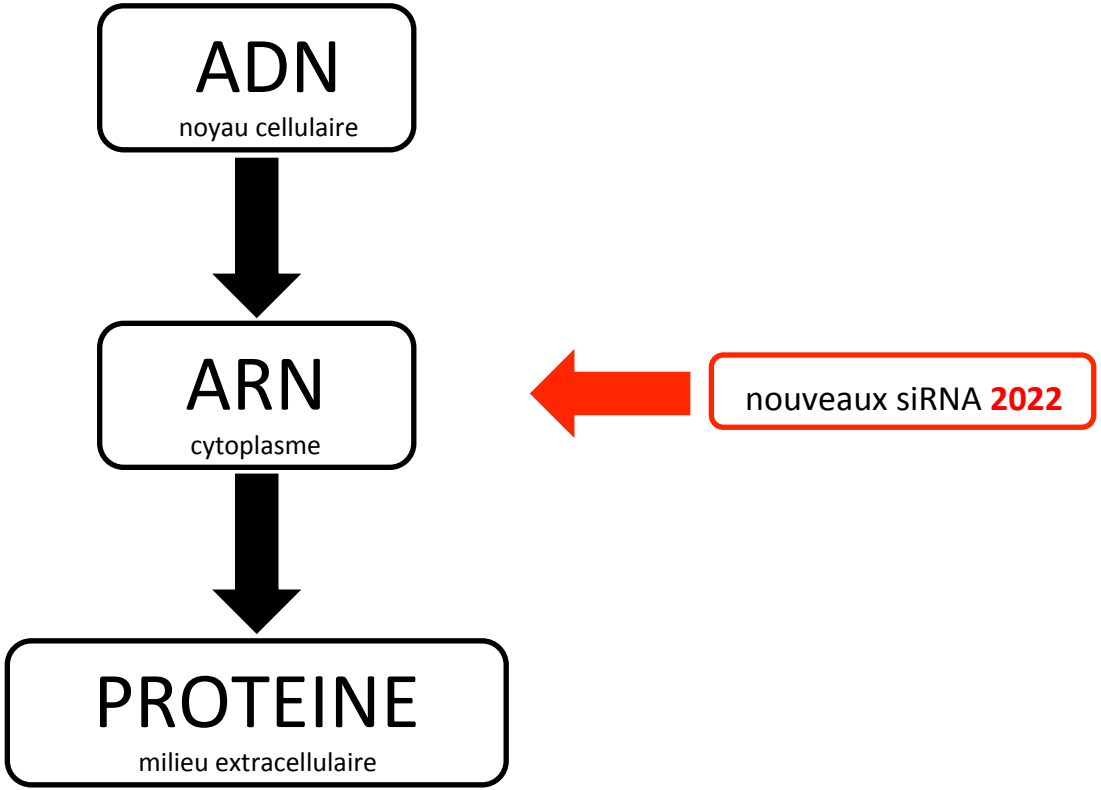
algorithme de traitement de la NAH-TTR en 2022



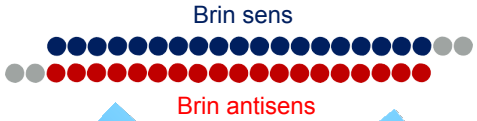


le futur proche & le futur plus lointain

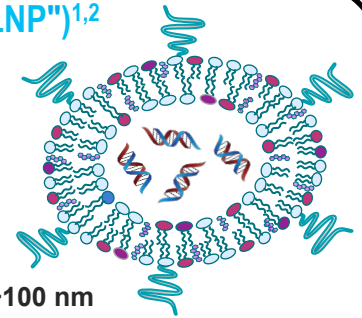
l'amylose héréditaire à transthyrétine



pARNi



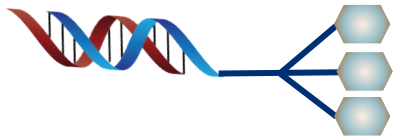
NanoParticules Lipidiques ("LNP")[1,2]

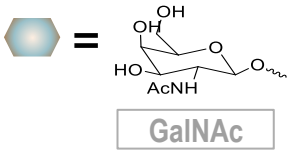


- Formulation lipidique de taille ~100 nm
- pARNi encapsulé
- Perfusion intraveineuse

Exemple du patisiran

Conjugué GalNAc-pARNi[3,4]





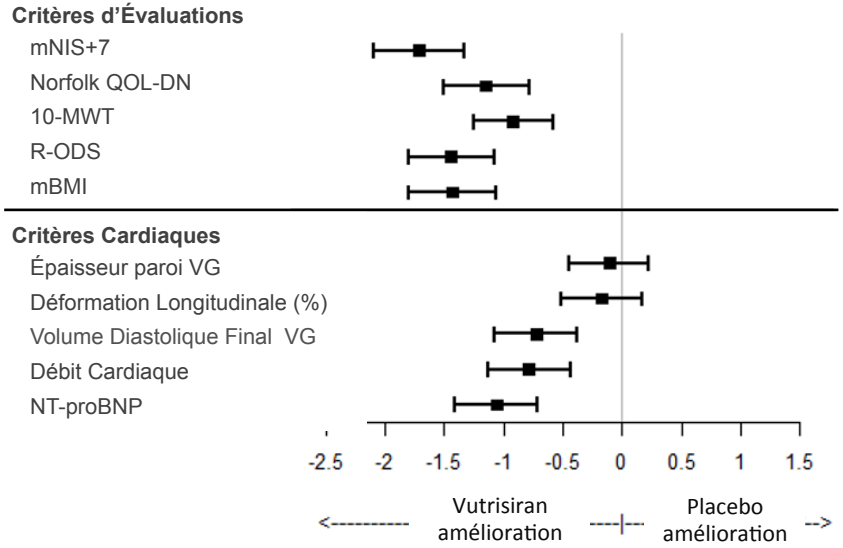
- Entité chimique unique
- Ligand GalNAc lié à un pARNi modifié
- Injection sous-cutanée

Exemple du vutrisiran

Similitude des résultats du vutrisiran (Helios A) et du patisiran (APOLLO)

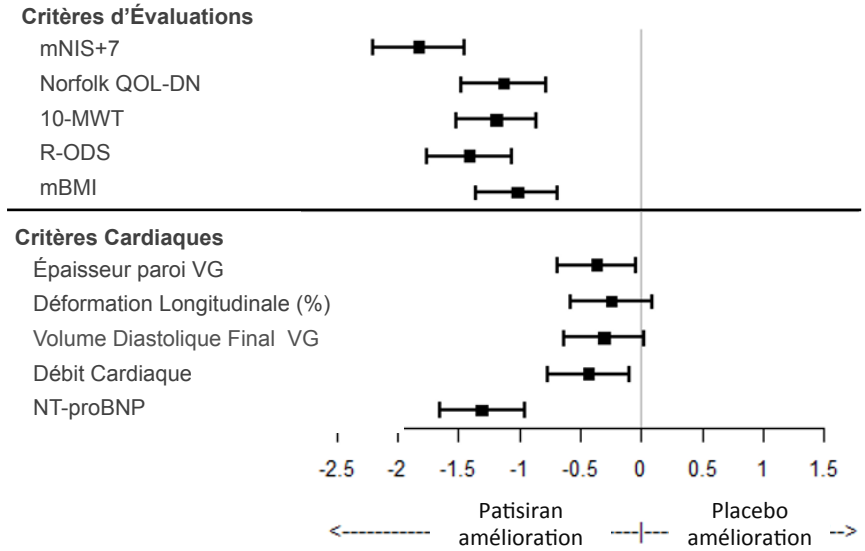
Efficacité du Vutrisiran[a] vs Placebo

Taille d'effet normalisée de l'étude HELIOS-A



Efficacité du Patisiran[b] vs Placebo

Taille d'effet normalisée de l'étude APOLLO

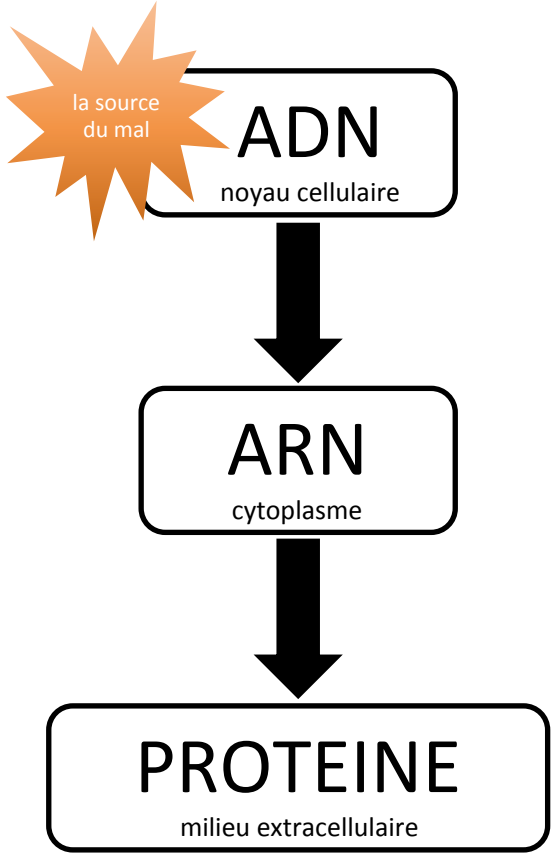


Cambridge MA, 14 juin 2022

- We want to inform you today of the U.S. FDA approval of AMVUTTRA™ (vutrisiran) injection, for subcutaneous use and indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adults.

- In HELIOS-A, the phase III pivotal trial, AMVUTTRA significantly improved polyneuropathy as measured by change from baseline in mNIS+7 compared with the external placebo group at 9 months. Please see full Prescribing Information for AMVUTTRA: AMVUTTRA Prescribing Information. Further details are described in the press release here: AMVUTTRA press release

l'amylose héréditaire à transthyrétine



CRISPR-Cas9 **2021**

CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis

Julian D. Gillmore, M.D., Ph.D., Ed Gane, M.B., Ch.B., Jorg Taubel, M.D., Justin Kao, M.B., Ch.B., Marianna Fontana, M.D., Ph.D., Michael L. Maitland, M.D., Ph.D., Jessica Seitzer, B.S., Daniel O'Connell, Ph.D., Kathryn R. Walsh, Ph.D., Kristy Wood, Ph.D., Jonathan Phillips, Ph.D., Yuanxin Xu, M.D., Ph.D., Adam Amaral, B.A., Adam P. Boyd, Ph.D., Jeffrey E. Cehelsky, M.B.A., Mark D. McKee, M.D., Andrew Schiermeier, Ph.D., Olivier Harari, M.B., B.Chir., Ph.D., Andrew Murphy, Ph.D., Christos A. Kyratsous, Ph.D., Brian Zambrowicz, Ph.D., Randy Soltys, Ph.D., David E. Gutstein, M.D., John Leonard, M.D., Laura Sepp-Lorenzino, Ph.D., and David Lebwohl, M.D.

New Engl J Med, 2021