

ÉVÉNEMENT HYBRIDE



Jeudi 18 décembre 2025  
Fondation Biermans-Lapôtre ■ PARIS

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# Futurs protocoles et essais cliniques en cours dans l'ATTR

Nicolas Piriou

CHU de Nantes – Centre de référence Cardiomyopathies



Centre de référence  
Cardiomyopathies

Journée organisée par :

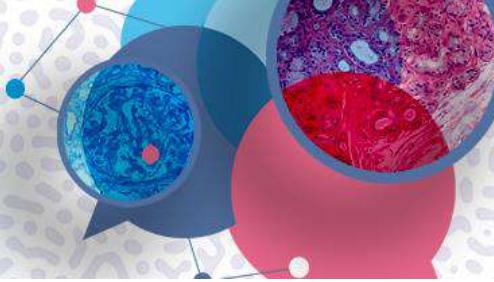


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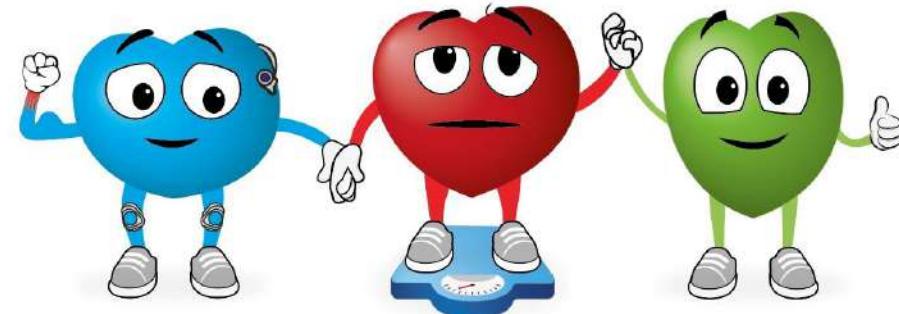


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## Liens d'intérêts

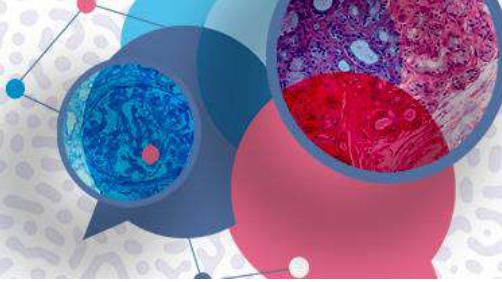
- Alnylam
- Pfizer
- Astra Zeneca
- Pfizer



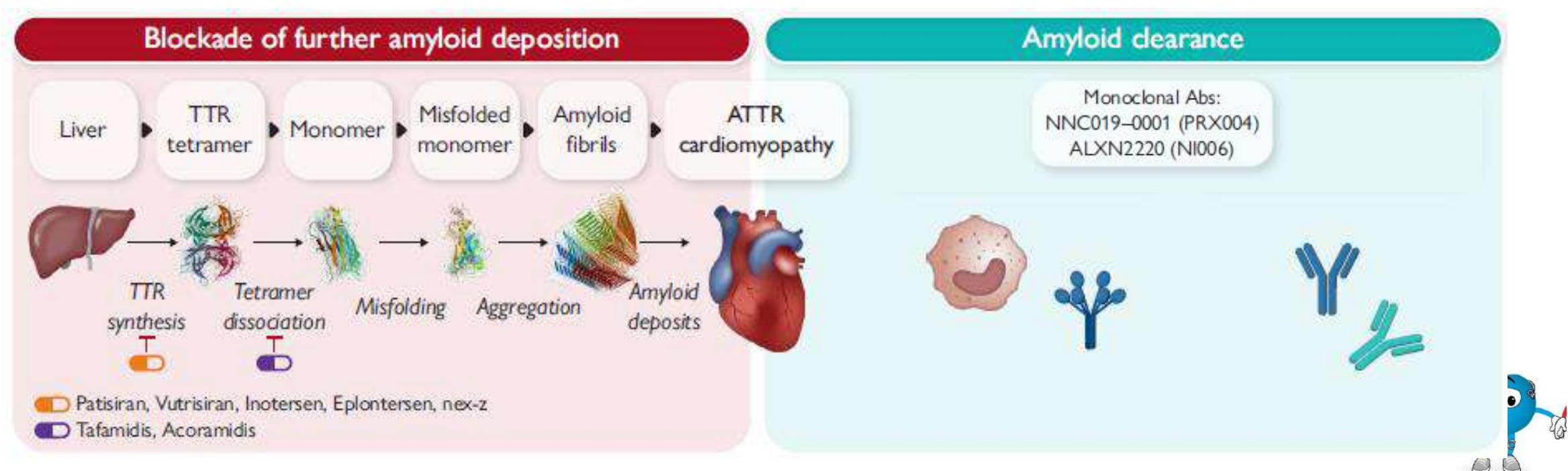
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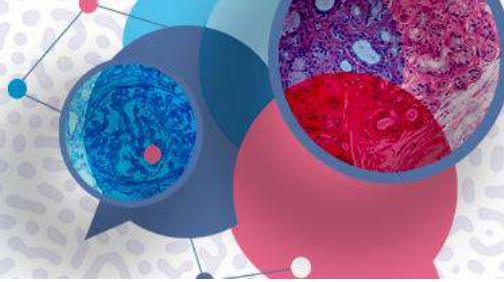
EPOF

EPON

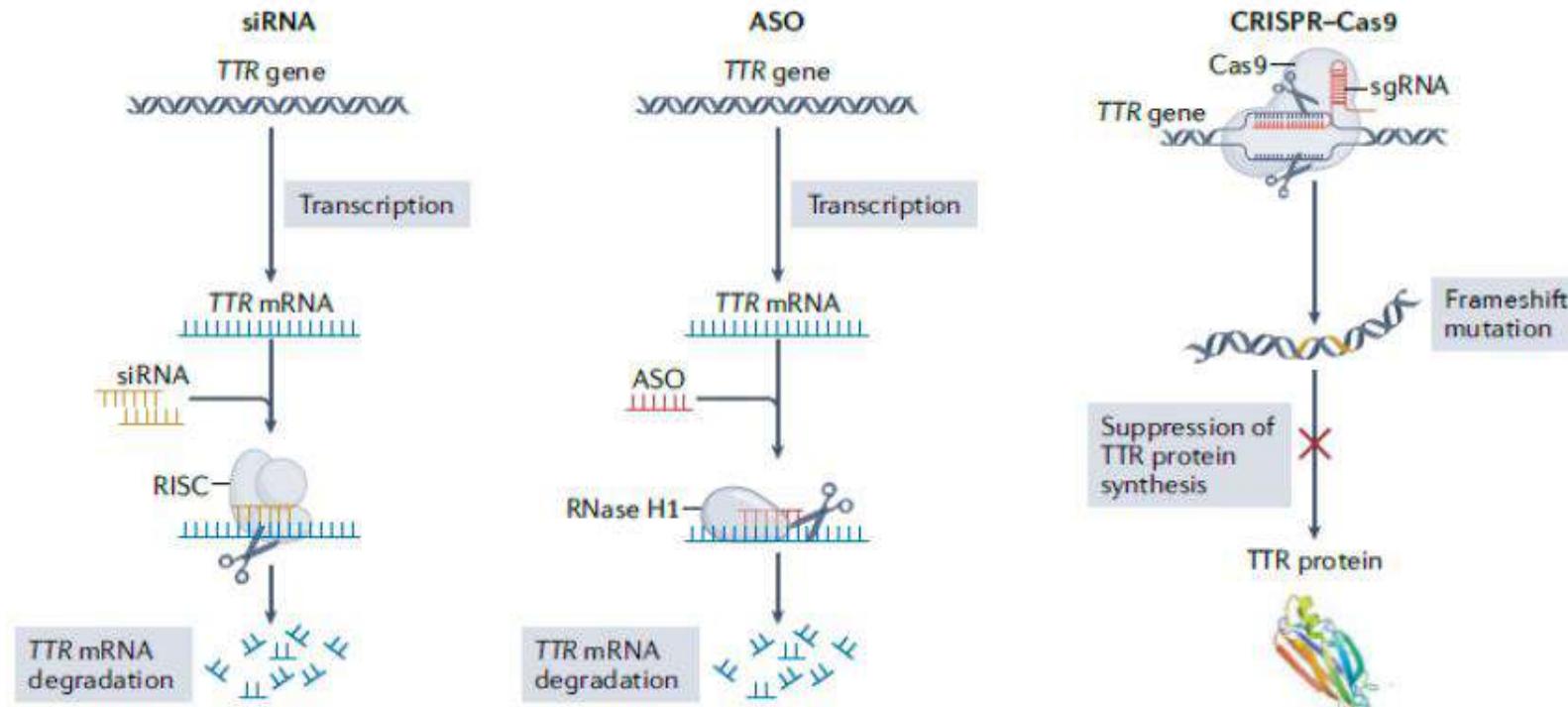
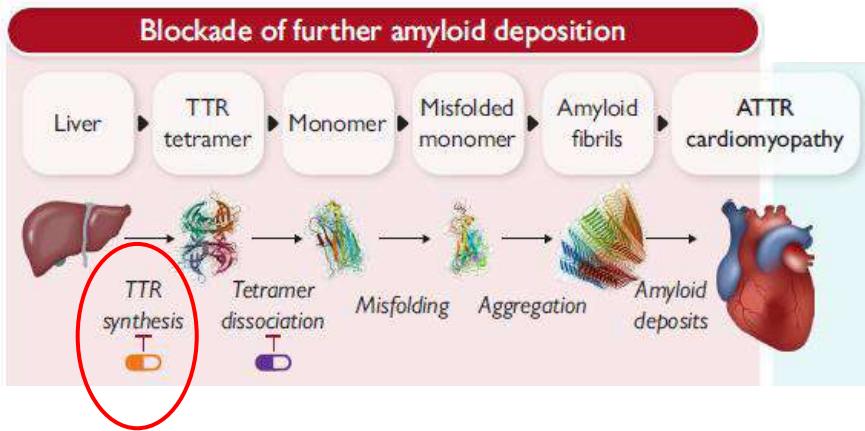


## Explorer de nouvelles voies thérapeutiques, de nouvelles molécules, de nouvelles stratégies



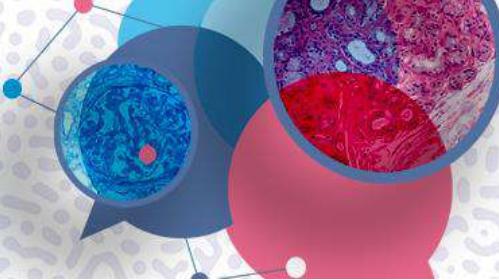


## Essais en cours sur la voie du Silencage TTR



*Nat Rev Cardiol.* 2022 Oct;19(10):655-667

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## CRISPR-Cas 9 TTR gene editing (Nexiguran Ziclumeran)

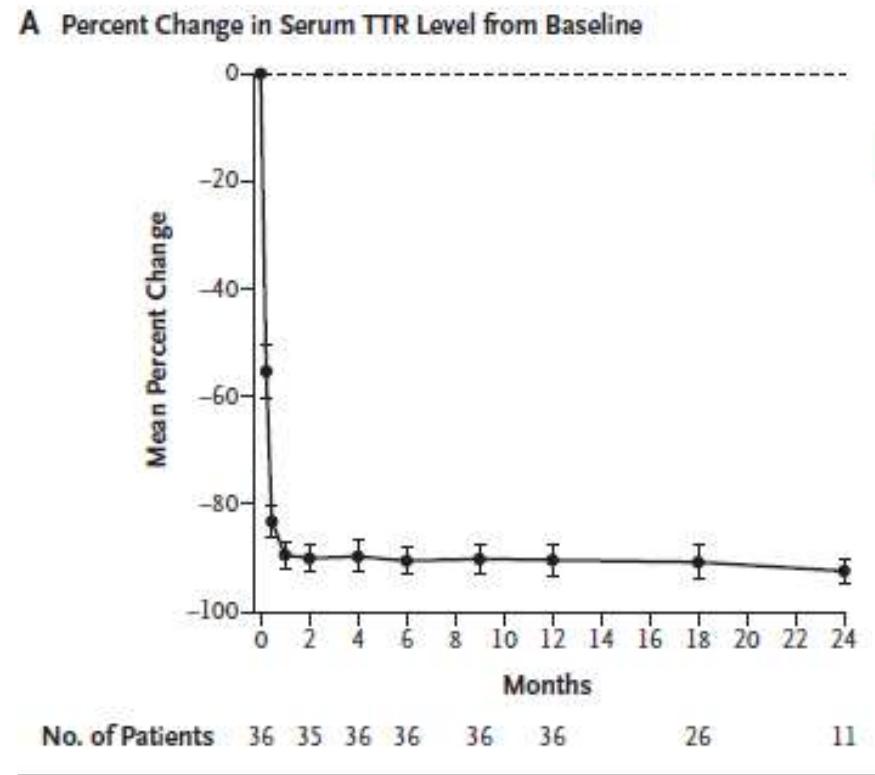
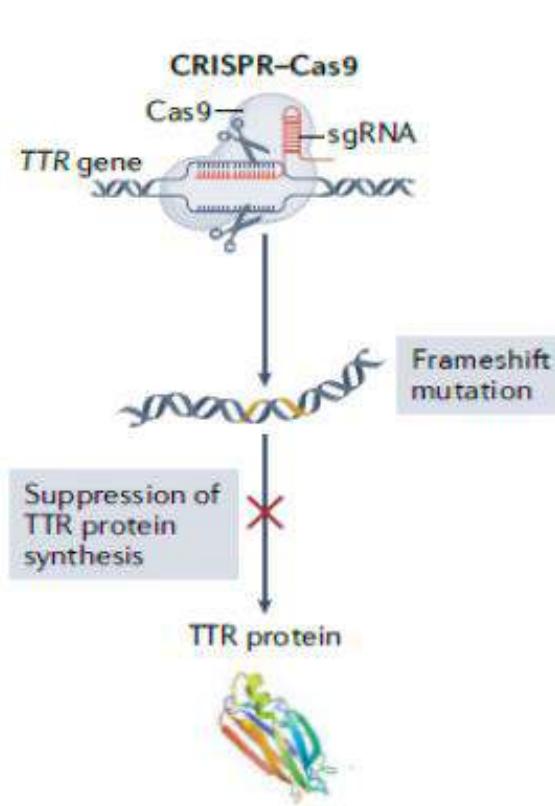
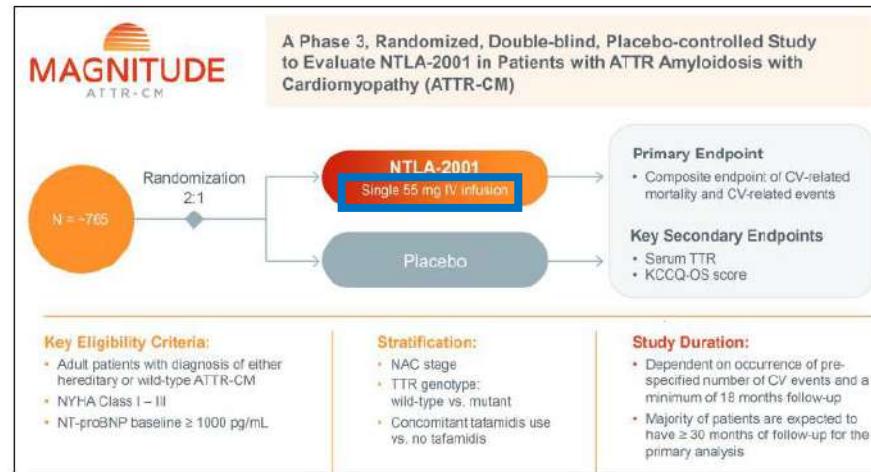


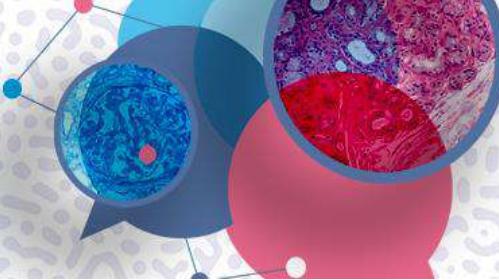
Figure 1. Reduction in Serum Transthyretin Level.

34 patients : 2 avec élévation des transaminases reliée au traitement

### Magnitude – Phase 3 Trial of CRISPR in ATTR-CA



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# Un nouveau siRNA : Nucreisan

Nucreisan is a synthetic siRNA conjugated to GalNAc, which enables highly efficient delivery to the liver.

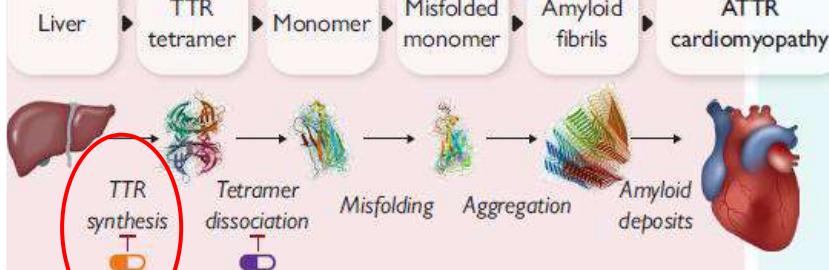
- GalNAc, a carbohydrate (sugar) molecule, is the ligand for the asialoglycoprotein receptor (ASGPR), which is highly and specifically expressed by hepatocytes.

Long-acting SC-administered GalNAc-conjugated siRNA targeting liver-expressed mRNA for TTR

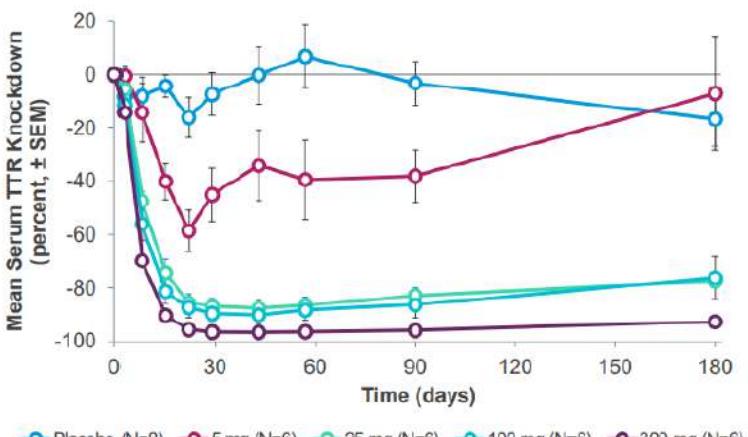
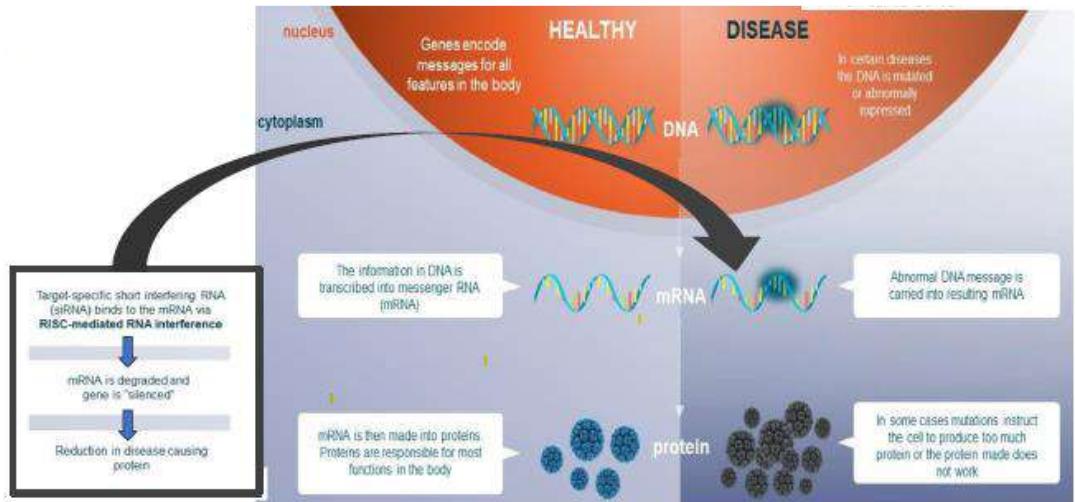


Alnylam

## Blockade of further amyloid deposition

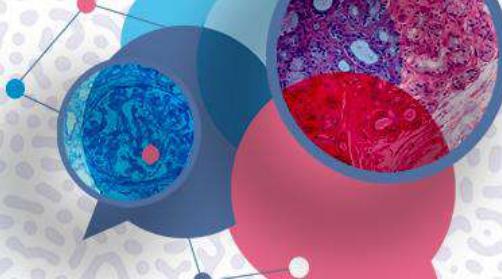


## Phase 1 data supports best-in-class profile

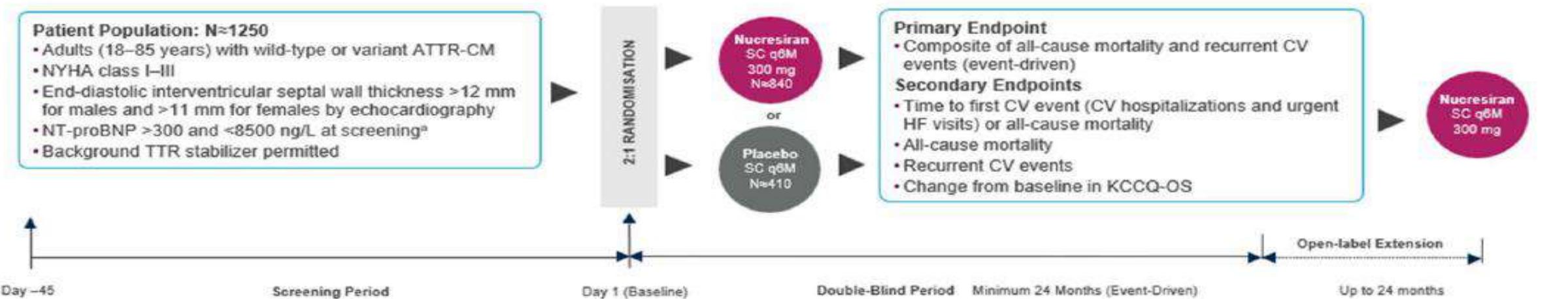


TRITON-CM  
ATTRON CLINICAL STUDY

- Single 300 mg dose resulted in rapid, deep, and durable TTR reduction:
  - >90% at Day 15
  - 97% at Day 29
  - 93% at Day 180
- Safety profile:
  - All doses of nucreisan have been **well tolerated**; no adverse events considered related to study drug by investigator
- Frequency of administration:
  - Data support **every 6 months** subcutaneous dosing



## TRITON-CM Study Design



### Other Key Inclusion Criteria

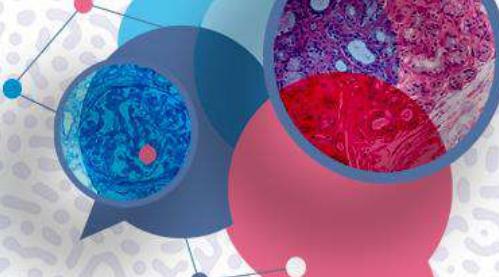
- Medical history of HF with ≥1 prior hospitalization for HF OR clinical evidence<sup>b</sup> of HF that requires treatment with a diuretic
- Demonstration of ATTR cardiomyopathy by one of the following:
  - Documented TTR amyloid deposits in cardiac tissue regardless of MGUS status
  - In the absence of MGUS, <sup>99m</sup>Tc scintigraphy with Grade 2 or 3 cardiac uptake
  - In the presence of MGUS, documentation of TTR protein in noncardiac tissue AND Grade 2 or 3 cardiac uptake on <sup>99m</sup>Tc scintigraphy

### Key Exclusion Criteria

- NYHA class IV HF; or NYHA class III heart failure AND ATTR Amyloidosis Disease Stage 3<sup>c</sup>
- Polyneuropathy Disability Score ≥IIIa at screening visit<sup>d</sup>
- Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m<sup>2</sup>
- Non-TTR cardiomyopathy, hypertensive cardiomyopathy, cardiomyopathy due to valvular heart disease, or cardiomyopathy due to ischemic heart disease
- Received prior TTR-lowering therapy OR plan for or anticipate beginning treatment during screening or the first 24 months following randomization

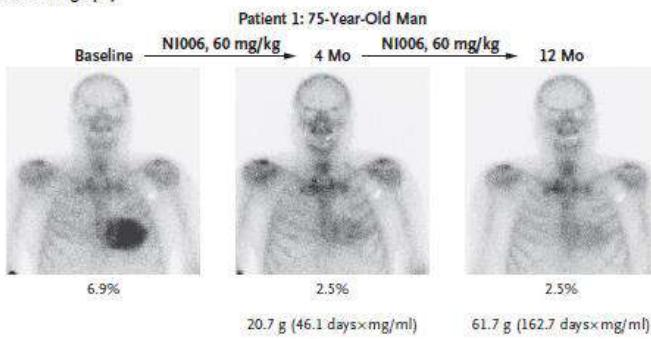
<sup>a</sup>NT-proBNP >600 pg/mL and <8500 pg/mL for patients with atrial fibrillation. <sup>b</sup>Manifested by signs and symptoms of volume overload or elevated intracardiac pressures.

<sup>c</sup>Defined as NT-proBNP >3000 ng/L and eGFR <45 mL/min.<sup>13</sup> <sup>d</sup>Requires cane or stick to walk or is wheelchair-bound due to polyneuropathy.

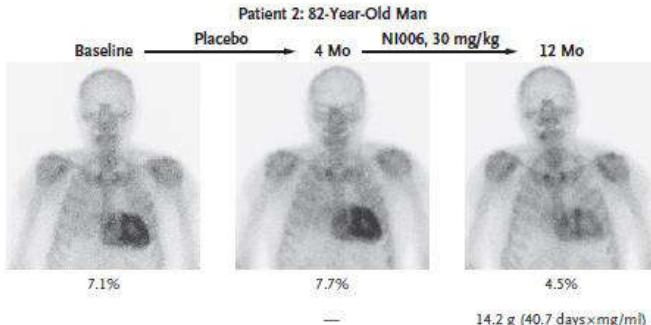


## La voie des Dépléteurs

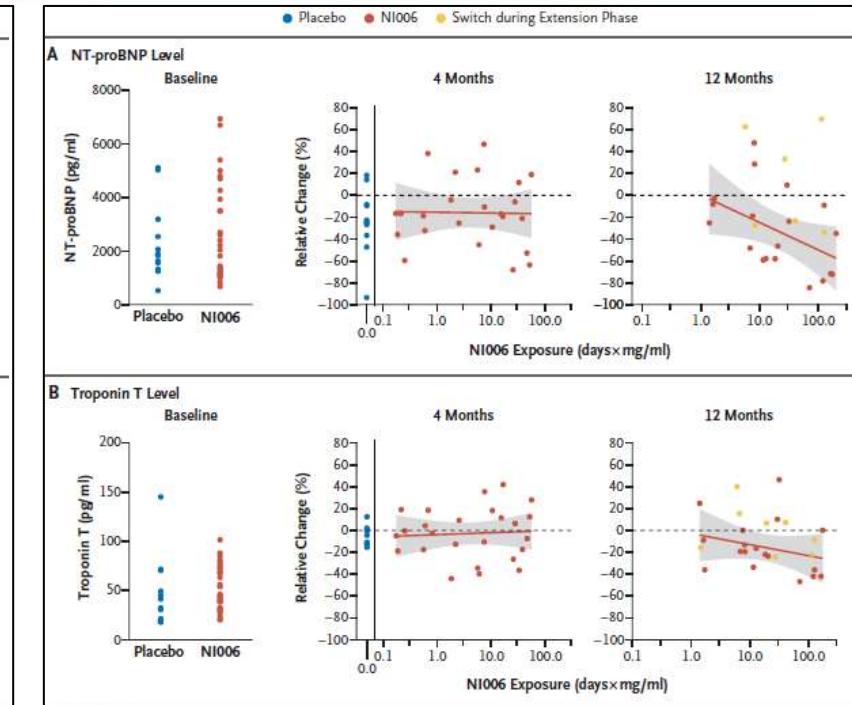
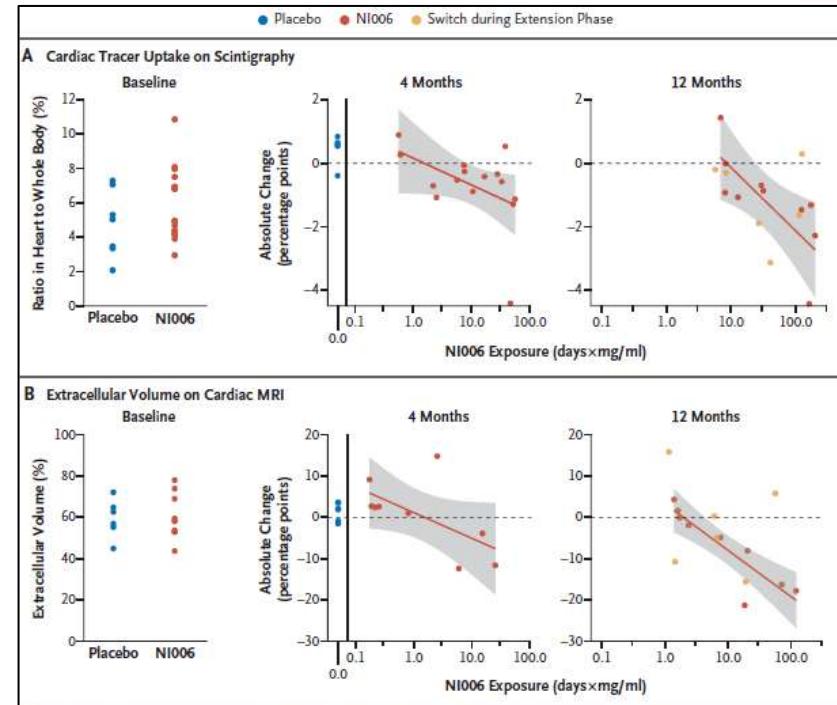
Cardiac Tracer Uptake on Scintigraphy



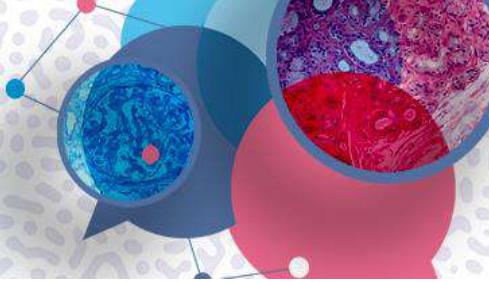
Ratio in Heart to Whole Body Total NI006



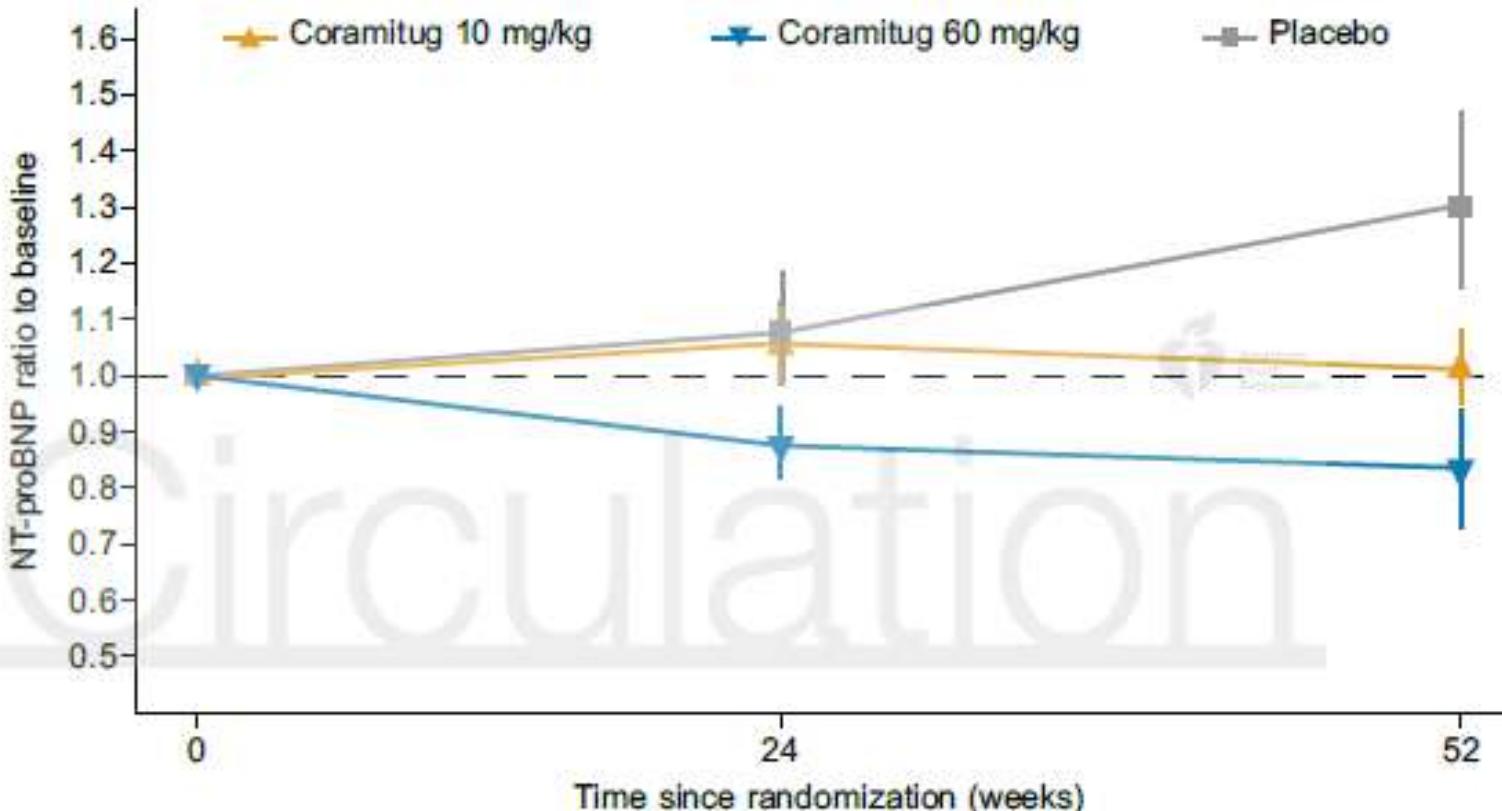
Ratio in Heart to Whole Body Total NI006



P.Garcia-Pavia et al. NEJM 2023



## Coramitug : données de phase 2



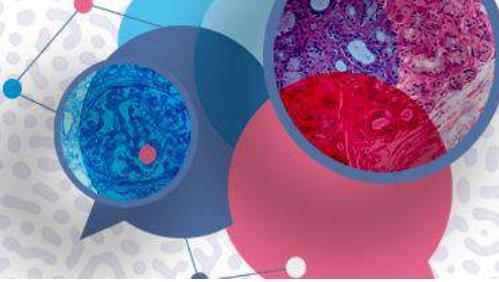
Pas de différence d'effet sur le 6MWT  
vs placebo



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M.Fontana et al. Circulation 2025

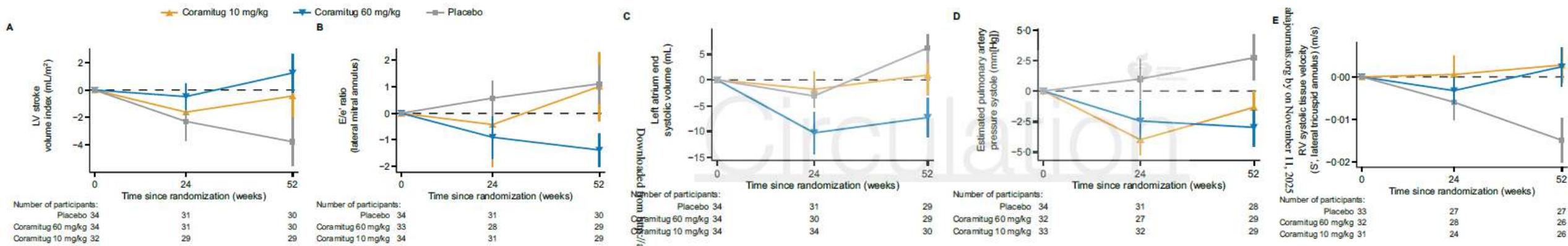
# 8<sup>e</sup> MASTERCLASS AMYLOSES CARDIAQUES



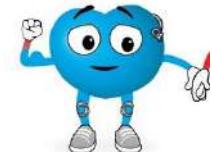
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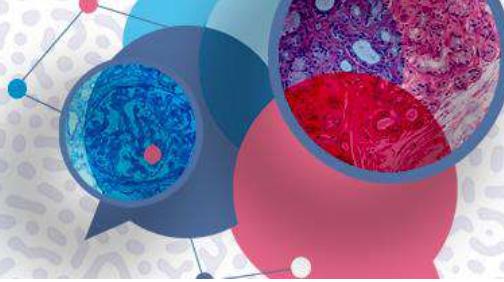


M.Fontana et al. Circulation 2025

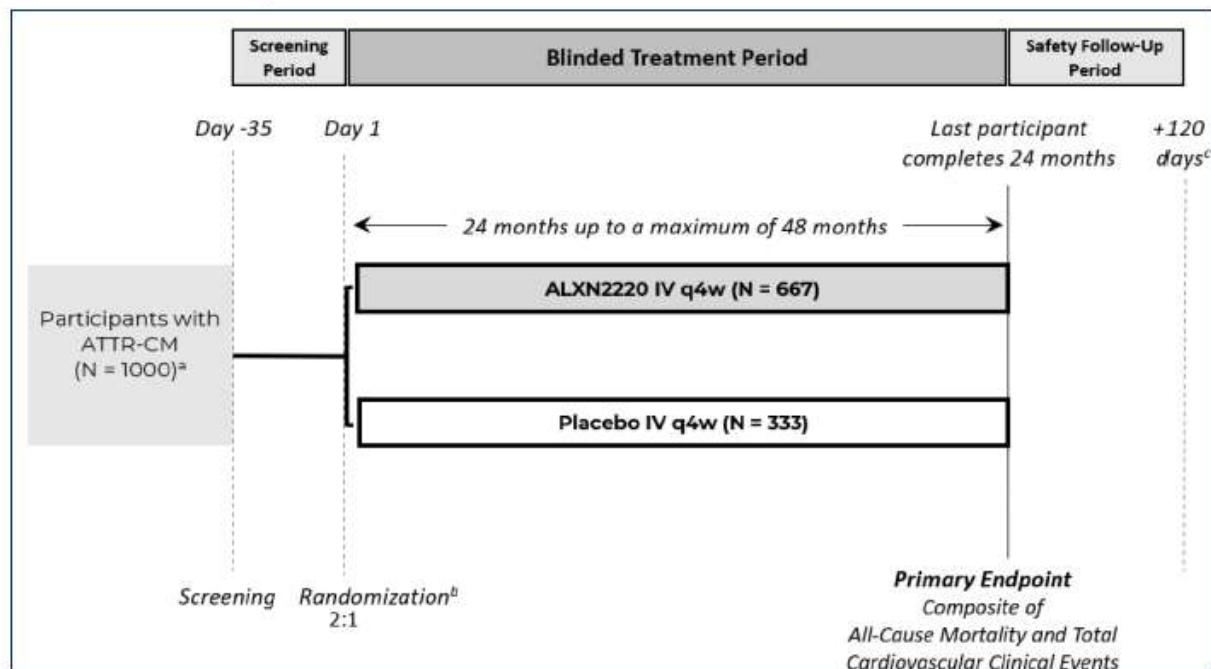


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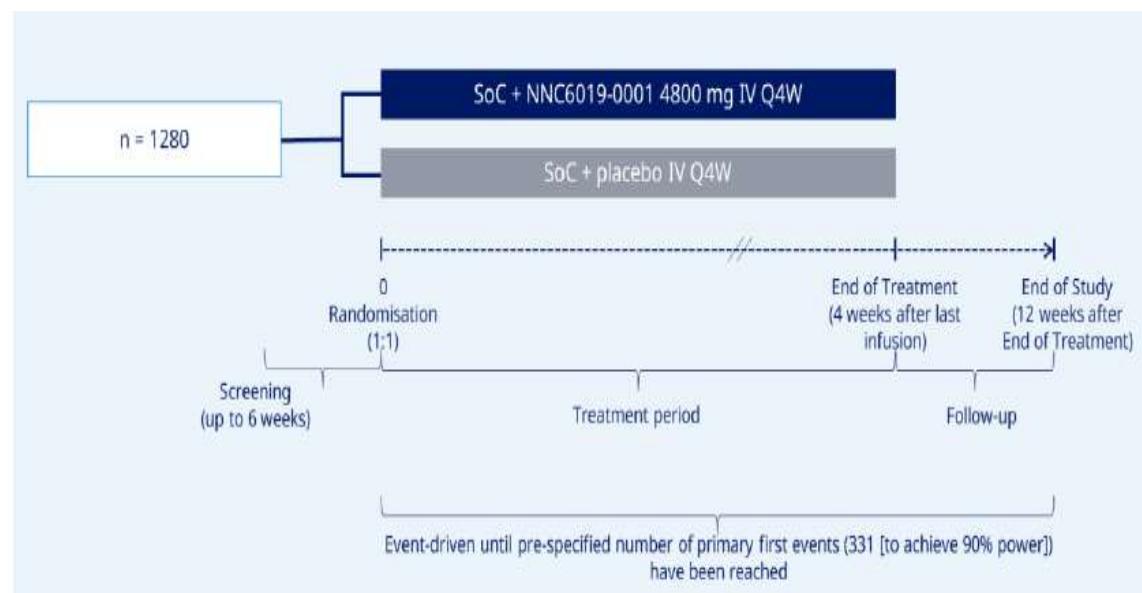


# Les Dépléteurs en Phase 3



**Acronym:** CLEOPATTRA

**Short Title:** CLEOPATTRA: A research study to look at the effects of treatment with a medicine called coramitug (NNC6019-0001) in people with heart failure due to ATTR amyloidosis.



## Primary objective

### Objective

To assess the efficacy of ALXN2220 in the treatment of adult participants with ATTR-CM by evaluating the difference between the ALXN2220 and placebo groups as assessed by the composite endpoint of all-cause mortality (ACM), and the total cardiovascular (CV) clinical events.

### Endpoint

Composite of all-cause mortality, and total CV clinical events during the blinded treatment period. (Anderson-Gill model with robust variance)

## Objectives

### Primary

To demonstrate superiority of NNC6019-0001 versus placebo, both added to SoC<sup>a</sup>, in reducing the CV death & morbidity in participants with ATTRwt-CM or ATTRv-CM

## Endpoints

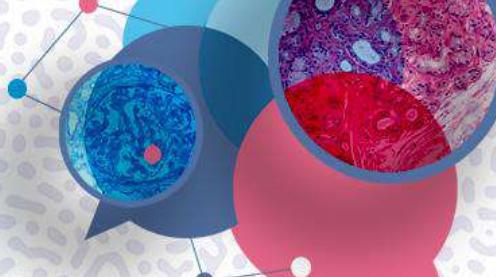
### Title

### Time frame

Primary:

- The composite outcome of:
  - CV death<sup>b</sup>
  - Recurrent CV events (CV hospitalisation<sup>b,c</sup> and urgent HF visits<sup>b</sup>)

From baseline (week 0) up to EOS<sup>d</sup>



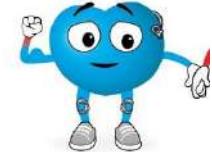
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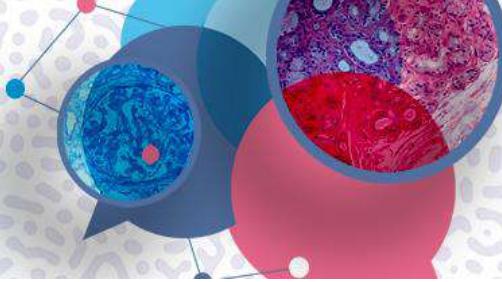
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# Les essais de Stratégie thérapeutique



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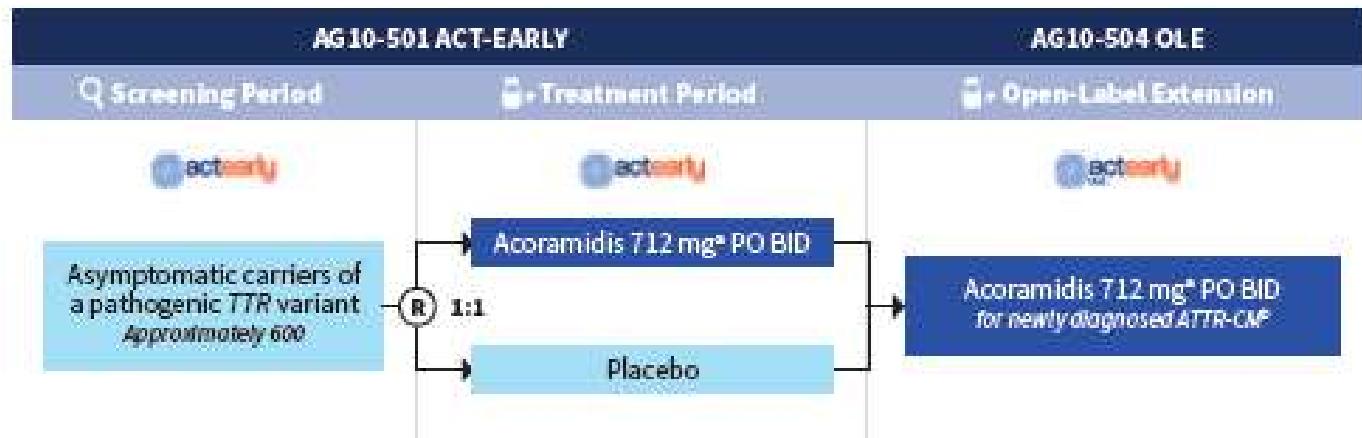
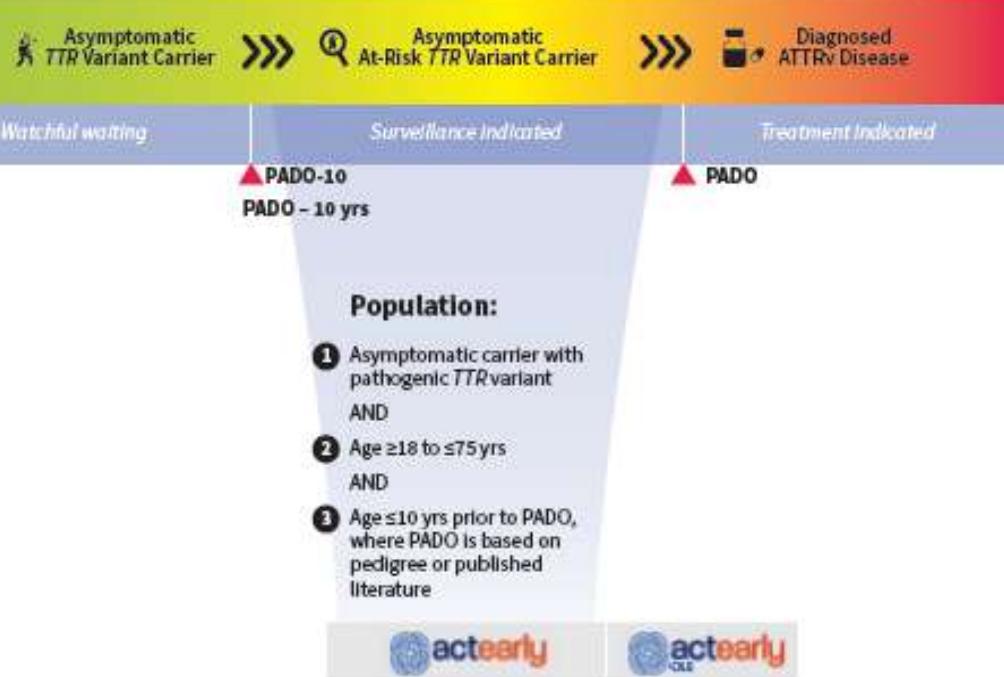
cardiogen  
filière nationale de santé  
maladies cardiaques héréditaires ou rares

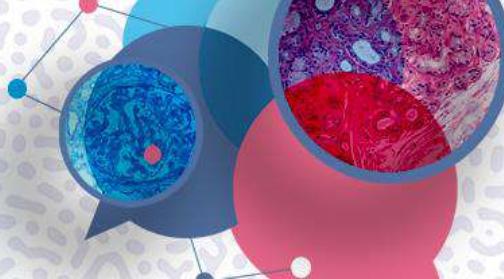


# Traitements PRÉ-SYMPOTOMATIQUE des apparentés porteurs du variant génétique pathogène

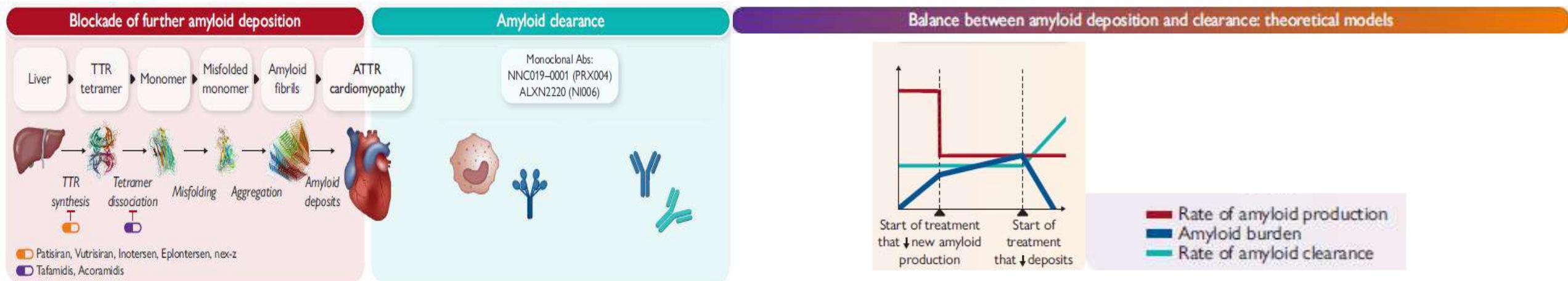
## Rationale and Design of ACT-EARLY, the Acoramidis Transthyretin Amyloidosis Prevention Trial

Pablo Garcia-Pavia<sup>1</sup>, Julian D. Gillmore<sup>2</sup>, David Adams<sup>3</sup>, Isabel Conceicao<sup>4</sup>, Teresa Coelho<sup>5</sup>, Daniel P. Judge<sup>6</sup>, Mathew S. Maurer<sup>7</sup>, Frederick L. Ruberg<sup>8</sup>, Scott Solomon<sup>9</sup>, Ahmad Masri<sup>10</sup>, Thibaud Damy<sup>11</sup>, Mariana Fontana<sup>12</sup>, Mary M. Reilly<sup>13</sup>, Nitasha Sarswat<sup>14</sup>, Peter van der Meer<sup>15</sup>, Mazen Hanna<sup>16</sup>, Morde Gertz<sup>16</sup>, Xiaofan (Martha) Cao<sup>17</sup>, Ted Lystig<sup>18</sup>, Uma Sinha<sup>19</sup>, Adam Castaño<sup>15</sup>, Leonid Katz<sup>15</sup>, Jonathan C. Fox<sup>15</sup>

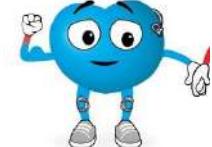




# L'arrivée des essais de COMBINAISONS thérapeutiques

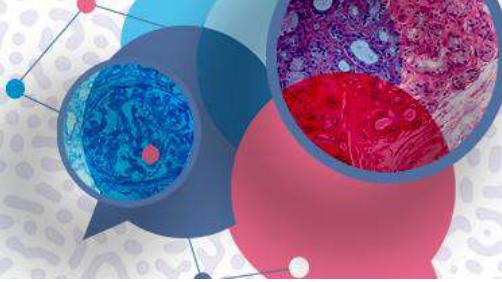


Adapted from M.Fontana et al. Eur Heart J 2025



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# 8<sup>e</sup> MASTERCLASS AMYLOSES CARDIAQUES



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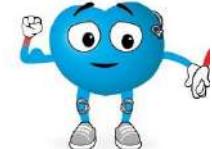
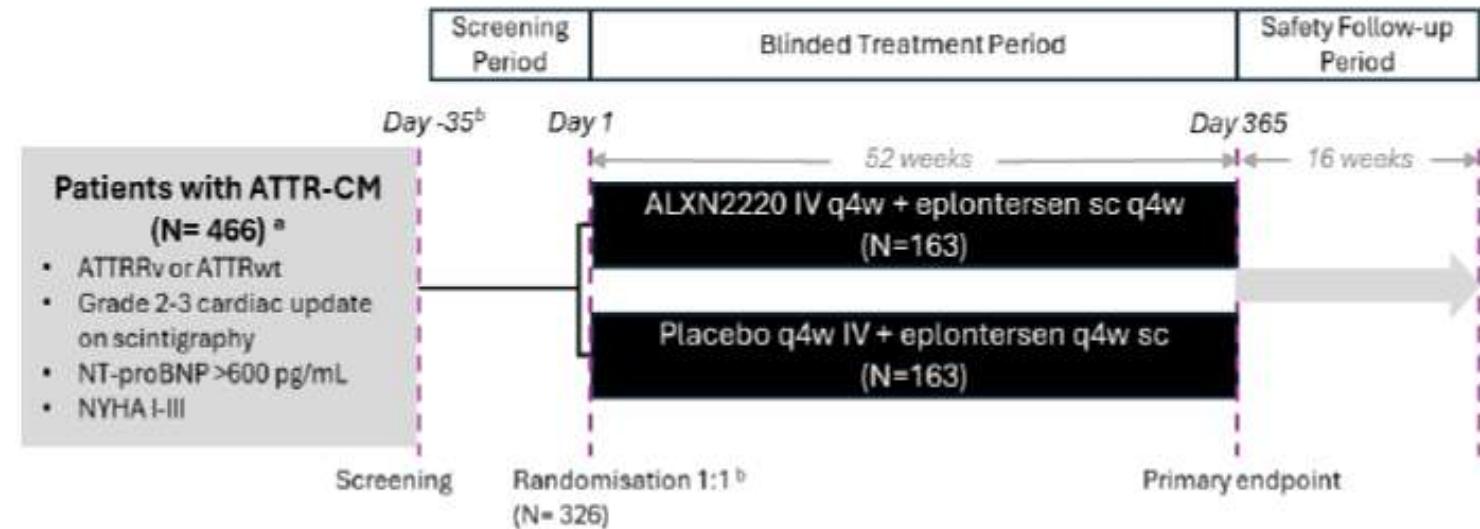


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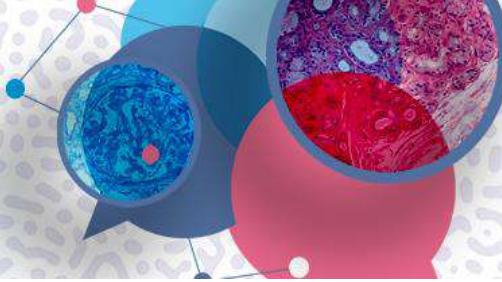
A Phase 2b, Randomized, Double-blind, Active-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Eplontersen and ALXN2220 Compared to Eplontersen and Placebo in Adult Participants with Transthyretin-Mediated Amyloid Cardiomyopathy (ATTR-CM)

Brief Title: Efficacy and Safety of Eplontersen and ALXN2220 for the Treatment of ATTR-CM



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maladies cardiaques héréditaires ou rares



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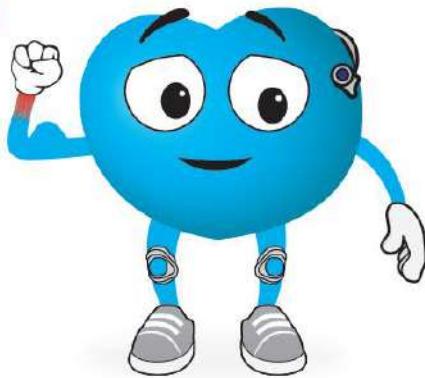


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Les atteintes rhumatologiques (synoviales) de l'amylose surviennent plusieurs années avant l'insuffisance cardiaque (EPOF)

R<sup>2</sup>EPOF

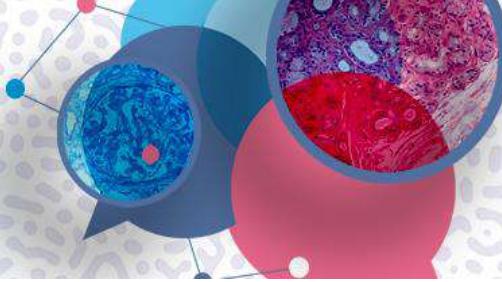
- Surdité
- Essoufflement
- Canal carpien
- Prise de poids
- Doigt à ressaut
- Œdèmes
- Rupture du tendon du long biceps
- Fatigue
- Canal lombaire étroit
- Prothèse de hanche/genou



Et si c'était une  
Amylose  
Cardiaque à  
transthyrétine ?



8<sup>e</sup>  
MASTERCLASS  
AMYLOSES  
CARDIAQUES



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*Il est temps de changer de **TAC-TIC**,*  
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